



## The Use of Totally Implanted Vascular Access Devices (Ports) in the Treatment of Atypical Hemolytic Uremic Syndrome in Children

Magdalena Mróz<sup>1</sup>, Katarzyna Krzyżak<sup>1</sup>, Anna Bogdał<sup>2</sup>, Hanna Woźny<sup>1</sup>, Martyna Bik<sup>1</sup>, Elżbieta Trembecka-Dubel<sup>3</sup>, Dagmara Roszkowska-Bjanid<sup>3</sup>, Maria Szczepańska<sup>1\*</sup>

<sup>1</sup>Department of Pediatrics, Medical University of Silesia in Katowice, Poland

<sup>2</sup>District Hospital in Zawiercie, Poland

<sup>3</sup>Department of Pediatric Nephrology with Dialysis Division for Children, Public Clinical Hospital No. 1, Poland

### Abstract

Totally Implanted Vascular Access devices (Ports; TIVAPs) are commonly used in oncological treatment in children. They are important for long-term therapy requiring continuous vascular access. The use of central catheters may also be extremely helpful in the therapy of children with chronic kidney diseases, such as atypical Hemolytic Uremic Syndrome (aHUS). In the past, the treatment of this syndrome required regular supplementation of fresh frozen plasma in the chronic phase of the disease, or substitution of red blood cells during relapse and plasmapheresis application. Eculizumab registered worldwide for the treatment of aHUS is injected intravenously every 2 weeks.

The manuscript presents a retrospective evaluation of the use of TIVAPs in 4 children treated due to aHUS. A total number of 6 ports was used, each  $4.3 \pm 1.7$  years of duration on average. Ten complications were reported, 30% of which included staphylococcal infections. Infections with encapsulated organisms were not recorded.

**Conclusion:** The use of vascular ports in children with aHUS seems to be safe provided that close monitoring and early detection of complications are carried out, allows to maintain repeated painless long-term access to the venous system, make available vascular preservation in patients with a significant risk for end-stage kidney disease.

**Keywords:** Totally Implanted Vascular Access devices (ports; TIVAPs); Atypical hemolytic-uremic syndrome; TIVAPs complications; Eculizumab

### Introduction

Totally Implantable Venous Access devices (ports; TIVAPs) are subcutaneous systems that provide permanent, easily accessible and long-term access to central veins. They are the most convenient and safest way of intravenous therapies for chronic diseases [1]. TIVAP consists of two basic elements: a catheter, which is inserted into one of the central veins, usually in the area of the clavicle, neck or arm, and whose tip is placed close to the opening of the superior vena cava to the atrium. The second element is the ventricle, connected to the catheter, placed under the skin [2]. The ventricle is equipped with the silicone membrane, which enables multiple punctures while maintaining the system tightness. It is estimated that the membrane strength ranges from 1000 to over 2000 punctures depending on the needles used [3]. Contraindications for TIVAP implantation include generalized infection, local skin lesions/inflammation, active vein thrombosis at the site of planned implantation, treatment with acetylsalicylic acid derivatives, clotting inhibitors and oral anticoagulants (when the treatment with low-molecular-weight heparin is necessary, its last dose should be administered at least 12 h before the planned procedure) [1]. The implantation should take place in the operating room with surgical sterility conditions. The procedure takes 30 min to 40 min on average. In children, the procedure is performed under general anesthesia. After implantation, chest X-ray is obligatory to assess the ventricular position, catheter path, position of the catheter tip and presence of possible hematoma or pneumothorax created during the complicated procedure. In most cases pneumothorax does not require drainage. The optimal position of the catheter tip (at the borderline of the superior vena cava and right atrium) reduces the risk of complications such as thrombosis or catheter occlusion [1]. The care of central access is the factor determining the

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#### \*Correspondence:

Maria Szczepańska, Department of Pediatrics, Medical University of Silesia in Katowice, ul. 3 Maja 13/15, 41-800 Zabrze, Poland, Tel: 48 32 3704305; Fax: 48 32 3704292;

E-mail: mszczepanska@sum.edu.pl

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incidence of infections. Although the use of fully implantable systems reduces the risk of complications compared to external catheters, septic complications are still a serious clinical problem [4,5].

With proper care, the TIVAP can perform its function for many years and bring an unquestionable convenience for patients. In addition to reducing the pain associated with frequent punctures, it also reduces the risk of local inflammation and the risk of the drug being vascularized. It enables the patient to move freely without the risk of accidental catheter damage, which is particularly important in children [6].

Permanent intravenous access is widely used, such as administration of chemotherapy, blood products, liquids, antibiotics, parenteral nutrition. The necessity of frequent and repeated long-term administration of the drug is the main indication of port implantation. For this reason, TIVAPs are used in oncological patients, patients with cystic fibrosis or chronic obstructive pulmonary disease as well as in palliative medicine [3]. In pediatrics, TIVAPs have been used in children with cancer and hemophilia requiring continuous administration of blood coagulation factors formulas.

The use of TIVAPs may also be extremely helpful in the therapy of patients with chronic kidney diseases, e.g. atypical Hemolytic Uremic Syndrome (aHUS). aHUS usually has a serious prognosis and multi-organ clinical symptoms may differ depending on the mutation found in a given patient [7]. In the past, the treatment of this syndrome required regular, long-term supply of fresh frozen plasma during the chronic phase of the disease or transfusion of red blood cell concentrate during relapse and plasmapheresis. In 2011 worldwide, and in 2018 in Poland, eculizumab, a humanized, monoclonal antibody directed against the C5 component of the complement system, which is also injected intravenously every 2 weeks, was registered for the treatment of aHUS [8,9].

This manuscript describes the course of aHUS treatment in four children using TIVAPs (Tables 1-3). All the parents have given informed written consent for TIVAPs placement and usage. According to the Polish law the Ethical Committee approval for this procedure was not necessary.

## Case Series

### Case 1

Atypical hemolytic uremic syndrome was diagnosed in a boy at 5 months of life. From the beginning the boy required renal replacement therapy (peritoneal dialysis continued further for 7 months) and repeated infusions of fresh frozen plasma. On day 21<sup>st</sup> during pneumonia, the disease was blown again with the need for ICU treatment and mechanical ventilation. On day 33<sup>rd</sup> the first TIVAP was established (size 4.5 Fr). On day 6<sup>th</sup> after insertion, the needle was accidentally punctured out from the port with edema of skin layers and hematoma formation. The condition was treated conservatively while maintaining the port's patency.

On the 41<sup>st</sup> day of hospitalization, again the child's condition deteriorated. After a double incident of cyanosis with saturation decrease to 70% and an increase in body temperature, as well as after finding elevated inflammatory markers the antibiotic ceftriaxone was applied empirically. A culture was taken from the TIVAP's blood sample and peritoneal fluid. Due to a positive result of the culture from the port - the presence of *Staphylococcus epidermidis* Methicillin-Resistant Strain (MRSE) - vancomycin was implemented.

Two weeks later (55<sup>th</sup> day of hospitalization), the boy underwent acute post-transfusion lung damage (TRALI) requiring another ICU treatment. The MRSE strain was cultured in the port blood sample collected on day 61<sup>st</sup> of hospitalization - therapy with teicoplanin followed by linezolid was implemented. The patient was discharged in good condition. A month later a third MRSE infection occurred, which was manifested by an increase in temperature, pale skin and chills. Due to the colonization of the TIVAP with MRSE, it was planned to remove the port in the antibiotic cover (vancomycin). A week later the patient was discharged home in a good general condition.

After three months (patient at the age of 14 months) it was decided to establish a new port due to the necessity of transfusion of plasma every 1 to 2 weeks. The procedure underwent without complications.

At the age of 2.5 years the patient was admitted to hospital due to fever up to 38.3 and vomiting. Similar symptoms occurred in the boy's brother the previous week. After performing additional tests, consecutive relapse of the underlying disease was diagnosed. A control blood culture from the port showed growth of MRSE and *Staphylococcus hominis* strains. After the application of vancomycin and topically urokinase, a sterile blood culture was obtained. The patient could return to standard aHUS treatment with plasma infusions every 2 weeks.

In December 2017 (age 2 years 8 months) the patient was qualified for treatment with eculizumab. The boy has been taking the preparation through the port regularly since December 21<sup>st</sup>, 2017, which resulted in the lack of subsequent symptomatic relapses of aHUS and improvement of his health. There were no TIVAP inflammatory complications on eculizumab.

### Case 2

Atypical hemolytic uremic syndrome was diagnosed in a girl at the age of 4. She did not require renal replacement therapy.

Initially treatment with plasma transfusions was undertaken. In the absence of remission plasmapheresis was implemented - 5 sessions were performed. After two months in remission after TPE, the girl was admitted to the ward due to aHUS recurrence.

The treatment with fresh frozen plasma infusions was started. 17 days later it was decided to establish the TIVAP. During the procedure the artery was punctured, which resulted in the formation of a hematoma in the area of venous confluence on the cannulated side. The patient did not report any complaints and the control chest X-ray taken after the surgery did not show any abnormalities.

The therapy was continued with regular plasma infusions for the next 2 years until the girl was qualified for treatment with eculizumab (at the age of 6 years), which is still administered through the TIVAP. The child remains in aHUS remission. There were no TIVAP inflammatory complications on eculizumab.

### Case 3

A 22-month-old girl was admitted with suspicion of typical HUS in the oligo-anuria phase. The child on admission was in a medium general condition, fatigue, pale and apathetic. The Tenckhoff catheter was inserted and peritoneal dialysis was started urgently and continued for 17 days. Thirty days later the patient had a relapse of aHUS. The girl was again in general medium condition, conscious but with limited logical contact, poorly responsive to stimuli. The treatment with plasma infusions and Therapeutic Plasma Exchanges

**Table 1:** Characteristics of the studied children with atypical hemolytic uremic syndrome.

	Patient 1	Patient 2	Patient 3	Patient 4
Age of diagnosis [months]	8	4	22	5
Current age [years]	5	9	10.5	10
Sex	M	F	F	M
Body weight at diagnosis [kg]	9.1	16	13	7.9
Height [cm]	75	104	97	69
Blood pressure at diagnosis SBP/DBP [mmHg]	125/72	107/60	80/60	130/100
Type of dialysis	peritoneal dialysis	None	peritoneal dialysis	peritoneal dialysis
eGFR at diagnosis [ml/min/1.73m <sup>2</sup> ]	9.31	66.61	17.11	6.41
Serum creatinine [μmol/l]	294	57	207	393
Hemoglobin concentration [g/dl]	6.4	5.8	7.7	8.2
Serum urea [mmol/l]	41	10.4	34.8	56.5
C3 [g/L]	0.77	0.84	0.93	0.68
C4 [g/L]	0.14	0.16	0.18	0.25
Platelets count [× 10 <sup>9</sup> /μl]	36	67	45	70
LDH [U/l]	783	813	1281	-
Hypotensive medication on admission	amlodipine, enarenal, acebutolol, clonidine, carvedilol, furosemide	furosemide, amlodipine	amlodipine, dihyralazine, furosemide	amlodipine, acebutolol
Current hypotensive therapy	amlodipine, ramipril, clonidine, metoprolol, carvedilol, furosemide	None	amlodipine, ramipril	amlodipine, ramipril
Underlying conditions	secondary hypertension, cardiomyopathy, hypothyroidism, history of pulmonary edema	secondary hypertension	Dandy-Walker syndrome, gallbladder stones, selective IgA deficiency	Allergies
Type of mutation	Mutation in the DGKE gene homozygous c.966G> A (p.Trp322*) Two variants of the CFH (H3) haplotype, heterozygous c.1204C>T and heterozygous c.-331C> T	Mutation in the CFHR1/CFHR3 gene homozygous for c.His402Tyr and c.-311C> T. Variants included in the CD46 heterozygote gene heterozygous c.-652A> G, heterozygous c.-366A>G, heterozygous c.* 783T>C, heterozygous c. 1127 + 638G>A and heterozygous c.989-78G>A	MCP gene mutation: heterozygous c.374T> G (p.Phe 125 Cys) and heterozygous c.491C>T (p.Pro 164 Leu). Mutation in the CFHR4 gene heterozygous c.917G>A (p.Gly306Glu). Mutation in the THBD gene heterozygous c.1418C>T (p.Ala473Val)	No mutations found

eGFR: Estimated Glomerular Filtration Rate. glomerular filtration according to the Schwartz formula; LDH: Lactate Dehydrogenase

**Table 2:** Eculizumab treatment.

Therapy	Patient 1	Patient 2	Patient 3	Patient 4
Treatment with eculizumab (Duration)	For 3.0 years	For 2.5 years	For 2.5 years	Eligible for treatment if another relapse occurs
Age at start of eculizumab therapy [years]	2.5	6	7	-
Symptomatic treatment before Eculizumab	FFP infusions	FFP infusions, TPE	FFP infusions, TPE	FFP infusions
Duration of use of plasma preparations	1 year 11 months	2 years 4 months	6 years 1 months	7 years 9 months
Current creatinine level [μmol/l]	88	27	38	57
Current eGFR [ml/min/1.73m <sup>2</sup> ]	42.7	169	132.6	89

FFP: Fresh Frozen Plasma; TPE: Therapeutic Plasma Exchange

(TPE) was applied with the improvement of girl's condition in following days.

After 10 months of remission another recurrence of aHUS in the course of respiratory tract infection, complicated by arterial hypertension and AKI occurred. In the following days the clinical condition was systematically improved, which allowed for symptomatic treatment of the girl without dialysis and therapeutic exchange of plasma. The vascular port was established at the age of 3 years. During the next 4 years, the patient regularly attended plasma infusions and follow-up examinations.

At the age of 6 years and 7 months the patient was admitted due

to vomiting. Thrombocytopenia and elevated renal function indices were observed. Plasma infusions, parenteral hydration, antibiotic therapy, antiemetics were applied. Due to increasing values of renal function parameters, hypercalcemia and decreased diuresis on the 2<sup>nd</sup> day of hospitalization; decisions were made to start hemodialysis as a matter of urgency. On the following days, therapeutic plasma infusions and hemodialysis procedures were continued. After 4<sup>th</sup> TPE the number of platelets increased to 113 × 10<sup>9</sup>/uL, so only plasma infusions were continued.

Due to the displacement of the catheter tip during the procedure of inserting the "acute" central catheter, the decision was made to remove the TIVAP (she used it for 3 years and 321 days).

**Table 3:** Overview of TIVAPs.

	Patient 1	Patient 2	Patient 3	Patient 4
Age of first implantation	9 months	4 years	3 years	3 years
Complications of TIVAP implantation	Three needle punctures with a hematoma formation, Three times a <i>Staphylococcus</i> infection	Arterial puncture with haematoma formation	Breathing disorders after general anaesthesia during the port insertion procedure	Port dislocation Bleeding from the puncture site
Total number of complications	6	1	1	2
Duration of use of the first port	2 months	For 4.5 years to the present	4 years	5 years
Cause of port removal	Infection of the port <i>Staphylococcus epidermidis</i> methicillin-resistant strain	-	Port dislocation	Replacement for larger
Duration of use of the second port	From 4 years to the present	-	From 3.5 years to the present	1 year (removed due to termination of treatment)
Total duration of vascular ports [years]	4 years 262 days	4 years 346 days	7 years 345 days	6 years 16 days

After 26 days, a new TIVAP was implanted. The control X-ray revealed the correct position of the port and no radiological symptoms of postoperative complications.

Less than a year after the procedure the patient was admitted due to acute gastroenteritis with suspicion of another aHUS relapse (eGFR =60.2 mL/min/1.73m<sup>2</sup>). Plasma infusions were administered at the rate of 2 transfusions/24 h, intravenous antibiotic therapy, antiemetics, analgesics and diuretics. The child's medium-heavy condition was recorded despite adequate diuresis. From day 5, the biochemical parameters were gradually improved, followed by the stabilization of clinical condition.

On February 2018 the patient was qualified for treatment with eculizumab (at the age of 6 years), which is still administered through the TIVAP. The child remains in remission of aHUS. There were no TIVAP inflammatory complications on eculizumab.

#### Case 4

Atypical hemolytic uremic syndrome was diagnosed in a boy at the age of 5 months - admitted at that time in the anuria phase. Three days earlier he had a fever up to 39°C, weakness, lack of appetite, aversion to drink and symptoms of gastroenteritis. Peritoneal dialysis (conducted during the first 5 days of hospitalization), symptomatic treatment and plasma infusions were initiated. Due to peritoneal dialysis catheter dysfunction and lack of effective dialysis fluid outflows, the renal replacement therapy had to be changed to hemodiafiltration. The course of disease was complicated by severe hypertension and pulmonary edema. In the following days, the clinical condition was systematically improved, which allowed to finish dialysis after 19 days of hospitalization. On day 36, the boy in good condition was discharged home.

Two years after the first hospitalization, the boy was urgently admitted to the hospital due to aHUS relapse. The week before the hospitalization weakness, rhinitis, coughing, fever and vomiting were present. Due to the need of TPE a central venous catheter was inserted under general anesthesia. After the procedure, breathing disorders occurred and the boy was transferred to the ICU.

To confirm the diagnosis percutaneous kidney biopsy was performed. The biopsy showed lesions corresponding to diffuse mesangial proliferative glomerulonephritis without features of microangiopathy.

Three months later the boy was admitted because of proteinuria to 3.9 g/l, diuresis limitation and thrombocytopenia during upper respiratory tract infection. Treatment with plasma infusions was started, without initiating steroid therapy - proteinuria was reduced,

platelet count was normalized. To ensure adequate venous access TIVAP was established. Due to the satisfactory clinical effect of plasma therapy, continuation of infusions every 21 days was planned.

Two and a half years later, antihistamines were recommended before the next transfusions due to an allergic reaction during the plasma infusion. Periodically, chest X-rays were taken to assess the position of the vascular port which did not show any abnormalities.

Four years and 11 months after the TIVAP was established, within the operating block, the TIVAP was replaced with a larger one with a diameter of 6.5 FR (to the right subclavian vein).

Three months later (2018), due to a remission of the underlying disease lasting more than 4 years, the boy was qualified for treatment with eculizumab only in the case of aHUS relapse and plasma infusions were also interrupted.

After another 10 months TIVAP was removed. The child currently remains in remission of aHUS.

## Discussion

In the chronic treatment of aHUS, eculizumab is currently used, administered intravenously every two weeks in infusion lasting 25 min to 45 min in adults and 1 h to 4 h in children [10]. Therefore, the use of central access in this therapy seems to be justified. Repeated necessity of venous access is burdensome for children due to their narrow veins, lower willingness to cooperate with the medical personnel and relatively easy possibility to damage the vein integrity [11]. This is particularly important in the youngest children and infants. Also in patients with a significant risk for ESKD, including patients with aHUS, vascular preservation would be very important, actually highlighted as the new "Save the Vein" initiative [12]. The TIVAPs increase patient's well-being during long-term treatment. They permit to avoid regular, frequent and painful punctures into the peripheral veins and related complications. They also facilitate the infusion itself. A single TIVAP can serve for many years.

In the assessment of the presented patients, it should be noted that all of them remained in aHUS remission after introduction of eculizumab. TIVAPs have been successfully used in current and previous plasma infusions therapies. This type of catheters is of great importance in the treatment of patients with diseases requiring chronic therapy such as aHUS or hemophilia, as it does not limit daily activity. aHUS patients might be at increased risk of infection vs. other patient populations using TIVAPs, mainly linked to applied complement inhibition. However, catheter infections including encapsulated organisms were not recorded during eculizumab

application in described patients.

Despite its high utility, the usage of TIVAPs is not free of complications. The cases in which the central venous catheter should be removed include TIVAP displacement, blood clotting without the possibility to be unblocked with the application of fibrinolytic drugs, improper size or colonization by bacteria [11,13-15].

Ten complications directly and indirectly related to the use of TIVAPs were observed in described by us children with aHUS. The commonest complication observed was hematoma formation. Hematoma in the subcutaneous pocket area is also the most common complication described in literature, occurring after port implantation [16]. To reduce the risk of hematoma formation directly after the procedure, ice packs are used. Analgesics and topical formulas containing heparin are used in the treatment [17].

All elements of the TIVAP are placed under the skin; no part is in contact with the external environment. This reduces the risk of infection spreading along the catheter, which is often a big problem with traditional methods of access to both central and peripheral veins [11,13]. Despite this, the incidence of infections may be even 4.1% [14]. Catheter-related infections may be directly related to patients' non-compliance or improper skin disinfection by patients and/or personnel [18]. They may be the reason for TIVAP removal. Catheter reimplantation may be performed no earlier than 7 days after the symptoms of infection have subsided and negative results of blood cultures have been obtained [17]. Beck et al. [19] evaluated the incidence of catheter infections at 7.4% in the cohort of 296 pediatric oncology patients (of which 128 ports were implanted). The most frequently isolated pathogens in blood cultures of oncological patients with catheter infections are Gram-positive bacteria, particularly coagulase-negative Staphylococci. The author's stress that these complications can be successfully treated [19]. Shim et al. [20] noted that 2.3% of ports were removed due to infections.

In patient 1, the TIVAP was colonized with Staphylococcus epidermidis strain, which involved additional hospitalization and antibiotic treatment burden, and finally removal of the TIVAP. The infections with this strain are the most common as it can migrate from the skin surface during injection [21].

One of the complications during catheter insertion was an arterial puncture with hematoma formation (patient 2). The use of ultrasound imaging during catheter insertion largely prevents such complications. They are relatively rare (frequency 0.2% in the retrospective cohort study of 500 cases) [22]. During catheter placement, patient 4 developed respiratory disturbances after general anesthesia. This may have been influenced by the patient's age - 3 years, general condition, underlying disease or previous infection. The incidence of airway complications under pediatric anesthesia is 7.87% and increases in children after recent airway infections and in children below 6 years of age [23].

One case of mechanical displacement of the TIVAP catheter tip after 3 years and 321 days of use was observed during insertion of the hemodialysis catheter, resulting in its immediate removal. The defective position of the TIVAP is not a frequently reported complication. The complication may occur in 1.3% to 5.4% of cases within 5 months of TIVAP insertion [1]. It may also occur after the time of use and be associated with patient growth [24]. It has been observed that TIVAP made of silicone and those of smaller sizes show greater flexibility, which may be associated with higher risk of

migration [18].

The use of TIVAP as a tool for quick and easy access to central veins of patients with aHUS for many years undoubtedly improves the comfort of their lives and facilitates chronic therapy. Pediatric patients and their caregivers should be given special care by the staff, ensuring that antiseptic agents and methods are used and the TIVAP is properly filled with anticoagulant. In addition, it is also very important to educate patients, their families and staff how to carry out procedures properly to prevent complications: Infections, clotting and mechanical injuries among them. Methods that can be used to reduce the number of adverse events, especially during port implantation, are radiological assessment of the chest immediately after surgery and imaging before its completion, or cardiac echocardiography for intravascular catheter tip observation.

## Conclusion

The usage of vascular ports in children with atypical hemolytic uremic syndrome seems to be safe provided that close monitoring and early detection of complications are carried out, allows to maintain repeated long-term access to the venous system, makes available vascular preservation in patients with a significant risk for end-stage kidney disease and minimizes pain associated with repeated punctures.

## Author Contributions

Formal analysis, Elżbieta Trembecka-Dubel, Dagmara Roszkowska-Bjanid; Investigation, Magdalena Mróz, Katarzyna Krzyżak, Hanna Woźny, Martyna Bik and Maria Szczepańska; Methodology, Elżbieta Trembecka-Dubel; Resources, Katarzyna Krzyżak, Hanna Woźny and Martyna Bik; Supervision, Elżbieta Trembecka-Dubel, Dagmara Roszkowska-Bjanid and Maria Szczepańska; Writing – original draft, Magdalena Mróz, Katarzyna Krzyżak, Hanna Woźny, Martyna Bik and Maria Szczepańska; Writing – review & editing, Magdalena Mróz, Anna Bogdał, Elżbieta Trembecka-Dubel and Maria Szczepańska.

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