RESEARCH ARTICLE
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Antimicrobial Lock Therapy: Is it a Real Savior in Pediatric Hematopoetic Stem Cell Transplant (HSCT) Patients?

Antimikrobiyal Kilit Terapisi: Pediatrik Hematopoetik Kök Hücre Nakli (HKHN) Hastalarında Gerçek Bir Kurtarıcı mı?

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Abstract
Objective: Central line-associated bloodstream infection (CLABSI) is a significant cause of morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT). Antimicrobial lock treatment (ALT), when utilized alongside systemic antibiotics, may be lifesaving when catheter removal (CR) is not feasible.
Materials and Methods: This retrospective study analyzed the clinical, laboratory, and microbiologic characteristics of CLABSI episodes of pediatric patients who underwent HSCT and applied ALT.
Results: There were 137 cases of CLABSI (63.5 male) who were given ALT. The median age was 48 (3-204) months. The most common causative microorganism was Gram-negative bacteria, encountered in 85 patients (62%). Forty-six patients (33.6%) had Gram-positive bacterial growth, whereas 6 had (4.4%) fungal infection. ALT was successful in 77.4% of the patients (n=106). CR was required in 25 patients (18.2%). The CLABSI-related mortality rate was 12.4%. When the outcome of ALT was evaluated, post-transplantation cyclophosphamide (PTCy) use, fungal growth, persistent bacteremia/fungemia, re-HSCT, inappropriate empirical antibiotic use, hypotension, and pediatric intensive care unit admission were significantly more common in the “unsuccessful” ALT group. The patients in the unsuccessful group had higher C-reactive

protein [110.2 (1.10-323.5) mg/L] levels when compared to the successful ALT group [58 (0.2-450.3) mg/L] (p=0.029). The presence of hypotension, HLA-mismatch transplantation, and persistent bacteremia/fungemia were independent risk factors for ALT failure.
Conclusion: ALT can be an effective catheter-saving strategy in HSCT pediatric patients. Nevertheless, patients should be monitored very closely during ALT, and the presence of certain risk factors should be taken into account.

Özet
Amaç: Kateter ilişkili kan dolaşımı enfeksiyonu (Kİ-KDE), hematopoietik kök hücre nakli (HKHN) alıcılarında önemli bir morbidite ve mortalite nedenidir. Sistemik antibiyotiklerle birlikte kullanıldığında antimikrobiyal kilit tedavisi (AKT), kateterin çıkarılması (KÇ) mümkün olmadığında hayat kurtarıcı olabilir.
Materyal ve Yöntemler: Bu retrospektif çalışmada, HKHN geçiren ve AKT uygulayan pediatrik hastaların Kİ-KDE ataklarının klinik, laboratuvar ve mikrobiyolojik özellikleri analiz edildi.
Bulgular: AKT verilen 137 Kİ-KDE olgusunun (%63,5 erkek) ortanca yaşı 48 (3-204) aydı. En sık neden olan mikroorganizma, 85 hastada (%62) karşılaşılan Gram negatif bakterilerdi. Kırk altı hastada (%33,6) Gram pozitif bakteri üremesi vardı, 6 hastada (%4,4) ise mantar enfeksiyonu saptandı. AKT, hastaların %77,4'ünde (n=106) başarılıydı. 25 hastada (%18,2) KÇ gerekli oldu. Kİ-KDE ile ilişkili ölüm oranı %12,4'tü. AKT'nin sonucu değerlendirildiğinde, nakil sonrası siklofosfamid kullanımı, mantar üremesi, kalıcı bakteriyemi/fungemi, rekürren HKHN, uygunsuz ampirik antibiyotik kullanımı, hipotansiyon ve pediatrik yoğun bakım ünitesine yatış "başarısız" AKT grubunda önemli ölçüde daha yaygındı. Başarısız gruptaki hastaların C-reaktif protein [110,2 (1,10-323,5) mg/L] seviyeleri, başarılı AKT grubuyla [58 (0,2-450,3) mg/L] karşılaştırıldığında daha yüksek bulundu (p=0,029). Hipotansiyon, HLA uyumsuz nakil ve persistan bakteriyemi/fungemi varlığı, AKT başarısızlığı için bağımsız risk faktörleriydi.
Sonuç: AKT, pediatrik HKHN hastalarıda etkili bir kateter kurtarma stratejisi olabilir. Bununla birlikte, hastalar AKT sırasında çok yakından izlenmeli ve belirli risk faktörlerinin varlığı dikkate alınmalıdır.
Anahtar sözcükler: Kateter ilişkili kan dolaşımı enfeksiyonu, pediatrik hematopoietik kök hücre nakli, antimikrobiyal kilit tedavisi

Introduction

Central line-associated bloodstream infection (CLABSI) is a significant cause of morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT). Approximately 27-68% of HSCT recipients experience CLABSI, with a rate of 12-25% increase in mortality [1-3].
CLABSI occurs when microorganisms form a biofilm layer inside the central catheter [4]. Overgrowing bacteria then enter the bloodstream and cause bloodstream infection. The intravenous antibiotic application cannot permanently eradicate the bacteria that adhere tightly to the central line (CL). Catheter removal (CR) is rational in that case. However, the CL is critical for several reasons, such as the application of chemotherapy, transfusion, parenteral nutrition, etc, especially in young children where vascular access is problematic [5].
Antimicrobial lock treatment (ALT), the application of an antimicrobial solution at high concentrations into the lumen of the CL for some time, is recommended to combat CLABSIs [6]. When utilized alongside systemic antibiotics, ALT may serve as a lifesaving approach whenever CL removal is not feasible. A continuum of access to CL, cost-effectiveness, and the capacity to provide high doses of effective antibiotics with minimal risk of systemic toxicity and resistance constitute some of the advantages of ALT [7]. On the other hand, it is also possible that ALT may raise physicians' thresholds for catheter withdrawal, resulting in prolonged treatment time or increased catheter-related complications (such as septic embolism).

Very few publications show the efficacy of ALT in pediatric oncology patients [8-12]. Data regarding the HSCT population, a particularly delicate group where infection control may be compromised rapidly, is even rarer [13]. The objective of the present study was to evaluate the characteristics and outcomes of ALT among pediatric HSCT patients with CLABSIs.

Materials and Methods

Study design

This study was conducted at a pediatric tertiary HSCT center in Istanbul, Turkey, between June 2018 and June 2022. The CLABSI episodes of HSCT patients were analyzed and the patients who received ALT were included in the study. The medical records of the patients were evaluated retrospectively.

Demographics, primary illnesses, the time since HSCT, immunosuppressive therapy, the presence of graft versus host disease (GvHD), CL-specific details, clinical and laboratory parameters at the onset of CLABSI, the course of the infection, components of antimicrobial treatment (systemic and ALT; the agent, dose, and duration) and the outcome were all documented.

To analyze the ALT-related adverse effects, complications such as bleeding, occlusion of the catheter, or possible antibiotic-related toxicity symptoms were also investigated.

Approval for the study was obtained from the Clinical Research Ethical Committee. Because of the study's retrospective nature, no informed consent was taken.

Clinical Setting & Central Line Procedure

Our facility comprises a 32-bed Hematology-Oncology and Pediatric HSCT unit that serves as a reference center for auto and allo-HSCT in Turkey. Since 2015, around 100 transplants have been performed each year. All allogeneic HSCT recipients are placed in single rooms with >12 air exchanges per hour and high-efficiency (>99%) particulate air (HEPA) filters capable of eliminating particles larger than 0.3 m in diameter. One nurse is assigned to every three transplant beds.

Preferably, the pediatric surgeon inserts double-lumen tunneled Hickman catheters routinely under elective conditions in the operating room before the HSCT protocol. Standard practices for catheter care include bathing every other day and cleaning the insertion site with chlorhexidine after every shower, followed by a suitable dressing change. When the catheter is not in use, a heparin lock (50 U in 5 mL heparinized saline) is applied once a week.

Definitions

According to the National Healthcare Safety Network (NHSN) of the Centers for Disease Control and Prevention (CDC) criteria, primary bloodstream infection in a patient with a CL and the isolation of a recognized pathogen with associated fever (>38 ºC), hypotension, and chills, on at least one blood culture or two or more blood cultures on separate occasions if a common skin contaminant was isolated, were accepted as CLABSI [14]. The growth of an organism in culture drawn from any catheter lumen (as a part of surveillance) in the absence of clinical findings was noted as “colonization”; these were excluded from the study.

To determine the efficacy of ALT, "no positive culture" of the same pathogen after 72 hours of treatment was the criterion. Persistent bacteremia/fungemia (after 72 hours of appropriate therapy) and the requirement of CR were accepted as “ALT failure”. “Relapse” was defined as the growth of the same pathogen in blood culture within three months.

Microbial identification

Patients with suspected CLABSI had paired blood culture samples obtained from the CVC (from each lumen of the catheter, in the presence of multiple lumens) and peripheral vein for microbiologic assessment. Following the collection of the blood samples, each one was appropriately labeled. Furthermore, taken into consideration was the differential time to positive, which states that an automated blood culture system detects growth in a culture of blood acquired through a catheter hub at least two hours before a culture of peripheral blood of equal volume that is drawn simultaneously. Catheter tip culture was also performed in the case of catheter removal. Following the manufacturer's recommendations, the bacteriological culture was performed using the BACT/ALERT® Blood Culture System (BIOMERIEUX, Durham, USA).

Samples from blood culture bottles with positive results were inoculated on 5% sheep blood agar, chocolate agar, and Eosin Methylene Blue (EMB) agar media. After an overnight incubation, samples were obtained from the purely grown microorganism colonies in the media, and pre-diagnostic procedures were completed. Advanced diagnostic and antibiotic susceptibility tests were initiated depending on the Gram stain, catalase, and oxidase test results. BD Phoenix TM Automated Microbiology (BD Diagnostics Sparks, MD, USA) was used according to the manufacturer's recommendations.

Management of the patients

In the HSCT unit, the antimicrobial treatment protocol in the suspicion of CLABSI included a systemic antipseudomonal antibiotic (piperacillin-tazobactam, cefepime, or meropenem) with a glycopeptide (teicoplanin/vancomycin). A specific agent may be preferred depending on the patient's prior infection and colonization state. In cases where there is hypotension or other signs of septicemia, vancomycin is favored over teicoplanin. Empirical therapy was adjusted according to the antimicrobial susceptibility results of the CLABSI pathogen. Bacteremia/fungemia is monitored by collecting blood cultures every other day.

Catheter removal is applied for patients with hemodynamic instability, persistent bacteremia, and non-improving clinical conditions despite adequate treatment. After removal, the catheter tip is sent for culture analysis.

ALT was utilized together with systemic therapy based on the culture sensitivity pattern of the isolated pathogen. In line with antimicrobial susceptibility, only one antibiotic was selected. Before ALT, the fill volume was calculated first. This was accomplished by flushing the line with normal saline and then withdrawing the content until blood was visible at the syringe tip. The amount to be administered was completed to the fill volume, ensuring the antibiotic concentration remained as recommended (Table 1). The ALT was applied to all lumens of the CVC. The ALT has been renewed based on the dwell time indicated in Table 1 [6,7, 11, 12]

The duration of antibiotic treatment varied depending on the causative microorganism: 7-14 days for Enterococcus spp., 10-14 days for coagulase negative Staphylococcus (CoNS), and 10-14 days for gram-negative bacilli [6]. After 72 hours of treatment, the control catheter and peripheral blood cultures were taken. All patients were followed for at least three months after the CLABSI episode.

Statistical analysis

Statistical analysis was performed with SPSS version 26.0 (IBM). The $\chi 2$ test and Fisher exact test compared categorical data. For variables not distributed normally, the Mann-Whitney U test was used. Significance was considered when $P < .05$. The most significant predictors of mortality by univariate analysis were chosen. Variables with a $P \leq .05$ in univariate analysis were chosen to perform a logistic regression analysis to estimate independent risk factors for unsuccessful ALT treatment.

Results

During the study period, 207 pediatric patients experienced CLABSIs, an incidence of 3.7/1000 catheter days. A total of 137 patients were given ALT together with systemic antibiotics.

Patient characteristics:

Of 137 patients, 87 (63.5%) were male. The median age was 48 (3-204) months. The underlying illnesses were thalassemia major [n=36, (26.3%)], acute lymphocytic leukemia [ALL; n=25, (18.2%)], severe combined immune deficiency [SCID; n=22, (16.1%)], aplastic anemia [n=18, (13.1%)], acute myeloid leukemia [AML; n=6, (4.4%)] and others [n=30; (21.9%)].

Auto-HSCT was performed in 19 (13.9%) patients, and full-matched donor (n = 68, %49,6), mismatch (n=35, %25,5), and haploidentical donor (n=15, %10,9) was performed in 118 patients. Twenty-eight (20.4%) patients had second HSCT.

Ninety (65.7%) patients had neutropenia with a median time of 9 (3-180) days at the onset of infectious episodes. Thirty-four patients (24.8%) had GvHD. Post-transplantation cyclophosphamide (PTCy) use was encountered in 47 (34.3%) patients.

CLABSI episode

The median duration from CL insertion to the day of infection (DOI) was 25 (3-252) days. The CL preference was Hickman in all patients. The most common causative microorganism was Gram-negative (GN) bacteria, encountered in 85 patients (62%). Forty-six patients (33.6%) had Gram-positive (GP) bacterial growth, whereas 6 had fungal infection (4.4%).

The median time of parenteral antibiotic use before ALT was 4 (2-11) days. Fifty-six patients (40.9%) had prior inappropriate empirical systemic antibiotic use. The antimicrobial regimen for lock therapy included meropenem (n=57, 41.7%), teicoplanin (n=27, 20.4%), vancomycin (n=13, 9.5%), colistin (n=13, 9.5%), ciprofloxacin (n=7, 5.1%), liposomal amphotericin B (LAM- B; n=6, 4.4%), tigecycline (n=5, 3.6%), linezolid (n=4, 2.9%), ceftazidime (n=4, 2.9%) and amikacin (n=1, 0.7%). Microbiologic distribution and ALT treatment are detailed in Table 2.

ALT was successful in 77.4% of the patients (n=106). CR was required in 25 patients (18.2%) due to persistent bacteremia/fungemia (n=18), unexplained tachycardia (n=2), and persistent hypotension (n=5). The median CR day was 3 (3-5) days. Six patients had relapse within three months. Adverse events that occurred during ALT were catheter displacement (n=2), occlusion (n=1) and skin tethering (n=1).

Comparison of CLABSI episodes according to ALT success

When the outcome of ALT was evaluated, there was no significant difference regarding the median age, gender, primary disease, presence and duration of neutropenia between the ALT successful and unsuccessful groups (Table 3).

PTCy use, fungal growth, persistent bacteremia/fungemia, second HSCT, inappropriate empirical antibiotic use, hypotension, and pediatric intensive care unit (PICU) admission were significantly more common in the "unsuccessful" ALT group. Likewise, the patients in the unsuccessful group had higher CRP [median 110.2, range (1.10-323.5) mg/L] levels when compared to the successful ALT group [median 58, range (0.2-450.3) mg/L] (p=0.029).

Considering ALT success, a double-lumen catheter was more common among the successful ALT group (p<0.001). The haploidentical human leukocyte antigen (HLA) match was significantly more common among the successful ALT group, whereas mismatch was significantly higher in the unsuccessful ALT group. The presence of hypotension, HLA-mismatch transplantation, and persistent bacteremia/fungemia were independent risk factors for ALT failure (Table 4).

Outcome

Twenty-four patients (17.5%) were admitted to the PICU, and 21 patients (15.3%) were given inotropes. Mortality occurred in 17 (12.4%) patients due to septic shock (n=7), acute renal failure (n=3), acute respiratory distress syndrome (n=3), arrhythmia (n=1), and pulmonary hemorrhage (n=2). The diagnoses of mortality cases was aplastic anemia (n=5), thalassemia major (n=4), SCID (n=3), AML (n=2), MDS (n=1), hemophagocytic lymphohistiocytosis (n=1), and non-Hodgkin lymphoma (n=1). Responsible microorganisms were K. pneumonia (n=11), A. baumanii (n=1), S. maucibalis (n=1), S. maltophilia (n=1), S .aureus (n=1), S. epidermidis (n=1) and C. albicans (n=1). The relapse rate within three months was 5.8%.

Discussion

Antimicrobial lock therapy, when used with systemic antibiotics, is an effective strategy to combat CLABSIs and salvage catheters. Although guidelines favor ALT, standardized prescriptions are lacking, particularly for children who underwent HSCT [6,15,16]. Thus, the decision to use ALT rather than CR is critical and mainly depends on the clinician's preference for this group of high-risk patients. Supporting this, being a bone marrow transplant recipient and having neutropenia were identified as risk factors associated with CR among children with varied illnesses [17, 18]. This study evaluated the ALT success rate among pediatric HSCT patients, contributing to the limited literature resources.

The CLABSI incidence was 3.7/1000 catheter days in the present study. This ratio is similar to the in the previously mentioned study which was 4.2/1000 catheter days [8]. However, the most prevalent microorganisms varied between these two studies. In the present study, GN bacteria, mainly K. pneumonia, predominated. The most common causative agent in that study was methicillin-resistant coagulase negative Staphylococcus (MR-CoNS) [8]. It has been noted that GP cocci, members of skin flora, have dominated in recent years [19,20]. Nonetheless, it is noteworthy that GNs have been reported in increased frequencies among children with malignancies, particularly in nations with limited resources [19-22].

In the present study, the successful ALT rate was 77.4%, which is within the range of previously reported (46%-86.6%) [8-10,13, 23]. These studies show variety in terms of diagnoses, catheter subtypes, ALT regimens or causative microorganisms. Similar to our study, Kurtipek et al. [23] reported a 75% success rate for ALT in their study, which included 182 pediatric patients with acute leukemia. In a pediatric HSCT report, Zanwer et al.[13] found the catheter salvage rate as high as 86.6% in the ALT-added CLABSI group, significantly higher than in patients without ALT. Similarly, Ohoro et al. [24] concluded that combining systemic antibiotics and culture-guided ALT was superior to the systemic antibiotic alone. In Tsai et al.'s [11] study, the overall success rate of ALT was 71.6%. When detailed, the success of ALT in Enterobacteriaceae infections (78.3%) was greater than that of CoNS (58.6%). Older age, elevated CRP levels, ALL as a primary disease, and candidemia were found to be the factors associated with ALT failure [11]. In a national study by Asrak et al. [25], the rate of success for ALT was found to be 68.8% among pediatric cancer patients. The study also found that younger age was an independent risk factor for the ALT failure.

In the present study, HLA-mismatch, second HSCT and PTCy use were significantly more common among the patients with unsuccessful ALT. This appears to be linked to HSCT failure, resulting in extended immunosuppression, hospitalization, and complications. According to recent research, PTCy was linked to higher rates of bacterial infections, regardless of the donor [26]. Furthermore, bacterial infections were associated with increased mortality rates [26].

On the other hand, Wolf et al. [9] reported that they were unable to find any advantage of using adjunctive ALT in pediatric oncology patients with CLABSIs. This is because the treatment failure rate was similar in both groups, i.e. the group that received only systemic treatment (ST, 38.4%) and the group that received ALT in addition to ST

(50%). Patients who received ALT had delayed CR and relapse of infection, resulting in later treatment failure. This study holds immense value as it stands in contrast to the opposing view presented in literature. The definition of treatment failure used in the study design is different from ours. In the study, treatment failure was defined as CR or mortality attributable to an infection within 14 days of the onset of CLABSI, or relapse of infection caused by the same microorganism species within 252 days. These variations in study design may have caused the difference. In their study, similar to ours, treatment failure due to CR within the first three days was significantly more common in the only ST group.

Guidelines recommend CR in the presence of S. aureus, P. aeruginosa, and fungemia [4,6]. However, inserting a new CL can be challenging, and the replacement significantly increases the risk of bloodstream infection and other issues depending on where the catheter is inserted (arterial puncture, pneumothorax, etc.) [27]. Furthermore, not all patients are eligible for catheter replacement. These include critically ill individuals who may be coagulopathic, thrombocytopenic or have restricted venous access [27,28]. In the present study, the ALT success rate for S. aureus and P. aeruginosa was nearly 91% and 88%, respectively. Despite the limited number of fungal ALT cases in our study, the success rate was far below the bacterial salvage ratio, 33.3%. We succeeded in two cases with C. albicans and C. parapsilosis-related CLABSI with L-AMB.

The literature contains very limited data on antifungal lock treatment [28-31]. In in-vivo studies with either fluconazole, echinocandin derivatives, or L-AMB (single or in combination), the therapeutic success rate varies between 17% and 100% [29-31]. In these studies, administered drug doses, the ingredients of lock solution, and dwell times vary significantly. Although ethanol-based lock solutions showed the highest activity, they were found to lead to potential risks, particularly concentrations above 28–30%, such as clotting, dizziness, protein precipitation, and compromised catheter integrity [29, 32]. We opted for heparin instead of using ethanol in any of the lock solutions. The potential risk of systemic circulation of heparin after application in small infants is a crucial concern [4]. Besides, there is some evidence that heparin might promote the formation of S. aureus biofilm, although this claim is not universally agreed upon [33]. In our experience, we did not observe any heparin-related side effects, and ALT produced an overall safe treatment profile.

The therapeutic success of L-AMB, reaching 83%, has also been reported in case series [29]. Castagnola et al. [34] reported a successful antifungal lock therapy experience related to C. parapsilosis CLABSI in an infant with L-AMB. Systemic antifungal treatment also included L-AMB for 14 days. Paul DiMondi et al [35] applied L-AMB lock therapy for C. albicans and succeeded in a 64-year-old female patient. However, they preferred micafungin as a parenteral agent. For our cases, we administered L-AMB both parenteral and as lock therapy.

Strengths and limitations of the study

It is important to acknowledge that our study has limitations as it is retrospective in nature. As with other studies on this topic, the preference and procedure of ALT rely on the clinician's judgment, as there are no clear guidelines in the literature. On the other hand, the current study has many strengths, such as the fact that it includes a special patient group, such as pediatric HSCT, the high number of cases, and it provides a broad perspective regarding microorganism diversity and antimicrobial drug experience.

Conclusion

To summarize, ALT can be an effective catheter-saving strategy in HSCT pediatric patients. Nevertheless, patients should be monitored very closely during ALT, and the presence of certain risk factors should be considered. We believe that, the results of this investigation will contribute to the architecture of further studies.

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Table-1. Antimicrobial regimens used for antimicrobial lock therapy

Antimicrobial agent	Antimicrobial concentration (mg/mL)	Heparin concentration (U/mL)	Dwell time (hr)
Vancomycin	5	2500	72
Teicoplanin	2	100	72
Meropenem	40	100	48

Colistin	15	100	48
Ceftazidime	10	2500	48
Ciprofloxacin	5	2500	48
Liposomal Amphotericin-B	5	100	12
Linezolid	4	5000	48
Tigecycline	10	100	48
Amikacin	5	5000	72

Table-2. Microbiologic distribution and characteristics of ALT treatment

Microorganism	n	Antibiotic use before ALT, d, median (range)	Antimicrobial drug (n)						Successful ALT, n	CR,n	The duration of ALT, d, median (range)	Mortality, n	Relapse, n
Gram-positive bacteria (n=46)			VAN	TEICO	LZD	TIG							
S. aureus	11	4 (2-8)	13	27	4	2			10	1	9 (5-13)	1	-
S. epidermidis	16	3 (2-7)	4	7	-	-			13	2	7 (4-12)	1	2
S. haemolyticus	7	4 (3-6)	3	12	-	1			5	1	7 (5-18)	-	1
C.indigelanous	4	3 (2-4)	4	2	1	-			4	-	8 (5-10)	-	-
E. faecium	3	5 (3-6)	2	2	-	-			3	-	10 (7-13)	-	-
S. capitis	2	3,4	-	-	3	-			2	-	10, 14	-	-
S. immitis	1	3	-	2	-	-			1	-	12	-	-
K. varians	1	2	-	1	-	-			1	-	10	-	-
M.luteus	1	4	-	1	-	-			1	-	7	-	-
Gram-negative bacteria (n=85)			MPM	COL	TIG	CIP	CEF	AMK					
K.pneumonia	31	4 (2-9)	20	8	2	1	-	-	20	8	10 (2-21)	11	3
A. baumani	10	4 (3-8)	7	-	1	1	1	-	7	3	7 (14-11)	1	-
E.coli	9	3 (2-5)	8	1	-	-	-	-	9	-	10 (6-21)	-	-
P. aeuriginosa	8	4 (2-7)	7	1	-	-	-	-	7	1	10 (5-17)	-	-
S. maucibalis	7	3 (2-4)	5	-	-	1	1	-	7		10 (5-15)	1	-
A. dentrificans	4	4 (3-6)	3	-	-	-	1	-	4	1	11 (7-14)	-	-
S. maltophilia	3	3 (2-4)	-	-	-	3	-	-	-	2	10 (5-15)	1	-
B. dimunata	2	3,4	1	--	-	-	-	1	2	-	7, 10	-	-
E. cloacae	2	2,3	1	1	-	-	-	-	2	-	5,14	-	-
O. antropi	2	3,3	2	-	-	-	-	-	2	-	7,9	-	-
E. meningoseptica	1	3	-	-	-	1	-	-	-	1	11	-	-
A. junii	1	2	1	-	-	-	-	-	1	-	10	-	-
P. florascens	1	2	1	-	-	-	-	-	1	-	9		-
A. ursinhi	1	2	-	1	-	-	-	-	1	-	4	-	-
S. marcescens	1	3	1	-	-	-	-	-	-	1	10	-	-
A.hidrophilia	1	3	-	1	-	-	-	-	1	-	9	-	-
P.putida	1	2	-	-	-	-	1	-	1	-	7	-	-
Fungi (n=6)			L-AMB										

C. albicans	4	5 (2-7)	4	1	3	8.5 (5-14)	1	-
C. parapsilosis	1	2	1	1	-	10	-	1
C. dubliniensis	1	4	1	-	1	7	-	-

The information that is presented was adjusted from references 6,7,11,12.
ALT; antimicrobial lock therapy, AMK; amikacine, CEF; ceftazidime, CIP; ciprofloxacine, CR; catheter removal, COL; colistine, LZD; linezolid, MPM; meropenem, VAN; vancomycine. The numbers under 'Antimicrobial drug (n)' indicate the number of treatments administered.

Table-3. Comparison of CLABSI episodes according to ALT success

Variables	**Successful ALT (n=106)**	**ALT failure (n=31)**	***p***
Age, mo, median (range)	48 (5-204)	64 (3-193)	0.14
Gender, male, n(%)	66 (62.3%)	21 (67.7%)	0.36
Post-transplantation Cy use, n(%)	29 (27.4%)	18 (58.1%)	**0.002**
Microorganism, n(%)			
Gram-negative bacteria	64 (60.4%)	21 (67.7)	0.45
Gram-positive bacteria	40 (37.7%)	6 (19.4%)	0.057
Fungi	2 (1.9%)	4 (12.9%)	**0.008**
Persistent bacteremia/fungemia, n(%)	5 (4.7%)	13 (41.9%)	**<0.001**
Second HSCT, n(%)	17 (16%)	11 (35.5%)	**0.018**
Inappropriate empirical antibiotherapy, n(%)	32 (30.2%)	24 (77.4%)	**<0.001**
Hypotension, n(%)	8 (7.5)	13 (41.9%)	<**0.001**
Catheter lumen number			
Double lumen	94 (88.7%)	4 (12.9%)	**<0.001**
Triple lumen	6 (5.7%)	4 (12.9%)	0.16
White blood cell count, cells/mm^3, median (range)	100 (10-12560)	100 (10-15090)	0.64
C-reactive protein, mg/L, median (range)	58 (0.2-450.3)	110.2 (1.10-323.5)	**0.029**
Procalcitonin, ng/mL, median (range)	0.085 (0.01-16.1)	0.09 (0.01-13.7)	0.89
PICU admission, n(%)	13 (12.3%)	11 (35.5%)	**0.003**
HLA match, n(%)			
Full-matched	57 (53.8%)	11 (35.5%)	0.07
Mismatch	21 (19.8%)	14 (45.2%)	**0.004**
Haploidentical	15 (14.2%)	0	**0.017**
Autologous	13 (12.3%)	6 (19.4%)	0.34

ALT; antimicrobial lock therapy, CLABSI; central line associated blood stream infection, Cy; cyclophosphamide, HLA; human leukocyte antigen, HSCT; hematopoetic stem cell transplant, PICU; pediatric intensive care unit

Table-4:Independent risk factors for ALT failure		
Variable	***p-value***	**Adjusted OR (%95Cl)**
Presence of hypotension	0.010	7,73 (1,63-36,51)
Mismatched HSCT	0.022	4,23 (1,39-23,61)
Persistent bacteremia/fungemi	<0.001	17,2 (1,6-134,5)
ALT; antimicrobial lock therapy, CI; confidence interval, OR; odds ratio		