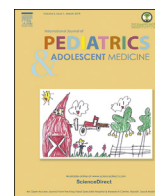


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International Journal of Pediatrics and Adolescent Medicine

journal homepage: <http://www.elsevier.com/locate/ijpam>

Original article

Clinical profile and outcome of antibiotic lock therapy for bloodstream infections in pediatric hematology/oncology patients in a tertiary care hospital, Karachi, Pakistan

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ARTICLE INFO

Article history:

Received 3 December 2018

Received in revised form

28 December 2018

Accepted 15 January 2019

Available online 29 January 2019

Keywords:

Antibiotic lock therapy

Bloodstream infections

Pediatric hematology/oncology patients

ABSTRACT

Background: Intravascular catheters are susceptible to infections, thus requiring catheter removal and leading to increased morbidity and costs. Antibiotic lock therapy (ALT) is a therapeutic technique that is used to salvage the catheter. The aim of this study was to evaluate the outcome of antibiotic lock therapy in bloodstream infections in pediatric hematology/oncology patients in a tertiary care hospital, Karachi. **Methods:** A retrospective review was performed from January 2013 to December 2017 of pediatric hematology/oncology patients with bloodstream infections and who received ALT at Aga Khan University Hospital. All cases of polymicrobial infections, catheter removal, or malfunction before the completion of ALT were excluded. Descriptive analysis was carried out using SPSS version 20.

Results: A total of nine hematology/oncology patients were eligible. The catheter was salvaged in 7/9 (77.8%) children, and in 2/9 (22.2%) cases, catheter was removed because of persistent bacteremia. The most common organism isolated was *Staphylococcus non-aureus* species (33.3%). Relapse with a similar pathogen occurred in 2 (22.2%) patients and 2 (22.2%) of them developed an exit-site infection.

Conclusion: In our experience, in almost two thirds of the cases, the catheter was salvaged, but disappointingly, relapses were high when the infection was due to *Staphylococcus* spp. Although this is a small study, our results show that ALT can be a potential safe adjunctive strategy to treat catheter-related bloodstream infections (CRBSI). However, we need larger prospective studies to test the safety and efficacy of ALT to develop specific ALT recommendations and guidelines particularly in children.

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1. Introduction

Catheter-related bloodstream infections (CRBSI) are a problem in both the developing and developed world [1–3]. An estimated 250,000 CRBSI occurred throughout hospitals in the year 2002 in the United States [4,5]. Antibiotic lock therapy (ALT) is a way to salvage the intravascular catheter, as it facilitates 100–1000 times greater killing of bacteria. Few studies have been carried out on this

subject in the developing parts of the world, but a majority of them were conducted in adult population and have a limited sample size. There are different types of intravascular catheters on the basis of the vessel it is inserted into (central venous, arterial, or peripheral), how it enters from the skin into the vessel (tunneled vs. non-tunneled), and the duration (long term or short term), etc. [6] These catheters can be used to administer intravenous fluids, medicines, parenteral nutrition fluids, and blood products. They also play an important role in monitoring the hemodynamic status and supporting hemodialysis [7]. Infection is a critical complication of intravascular catheters that leads to increased morbidity and healthcare costs. ALT should always be used in combination with systemic antibiotics. Contraindications to ALT include an exit/tunnel infection, complications such as endocarditis, or hemodynamic instability [7]. The most common groups of microorganisms causing CRBSI are coagulase-negative staphylococci, *Staphylococcus*

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Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

aureus, and enteric gram-negative bacilli. IDSA guidelines currently recommend catheter removal in cases of infections caused by *S. aureus* and gram-negative bacilli. The antibiotic selected for the lock solution should cover common, or preferably the targeted, pathogens, should be stable and be able to penetrate the biofilm, and have a reasonable side effect profile. Vancomycin and gentamicin are the antibiotics for which the largest amount of data is available, but many other antibiotics have also been evaluated in clinical use [8].

CRBSI can lead to the removal of catheters, thus leading to not only increased morbidity and cost but also loss of vascular access, which is problematic particularly in the pediatric population. ALT enables the use of a high-concentration antibiotic without systemic toxicity or the need to monitor serum levels of antibiotics [9,10]. However, because of limited evidence of the use of ALT in children, there is a need to identify the appropriate dose, duration, and outcome of ALT in children [11]. The aim of this study was to evaluate the outcome of ALT in bloodstream infections in pediatric hematology/oncology patients in a tertiary care hospital, Karachi.

2. Methods

A retrospective study was conducted from January 2013 to December 2017 in the department of pediatrics and child health. All hematology and oncology patients of age ≥ 1 year and either gender with bloodstream infections and having received ALT were included. Children with polymicrobial infections whereby the catheter was removed before the completion of ALT were excluded. Data were collected on participants' demographics, medical history, primary diagnosis, treatment, laboratory parameters, and outcome of ALT on a structured proforma. All the individuals were followed up for a period of 1 month after the completion of ALT to assess the relapse rates. Descriptive analysis was carried out using SPSS version 20. Data were expressed as frequency and percentage for categorical variables such as gender, primary diagnosis, antibiotic used for lock therapy, pathogen isolated, relapse, persistent bacteremia, and mortality. For quantitative variables such as age, days, dose and volume of ALT, and length of hospital stay, data were expressed as mean $\pm$ SD or median $\pm$ interquartile range depending on data distribution. The chi-square test was used for comparing qualitative variables, and the *t*-test was used for comparing quantitative variables.

3. Results

A total of 9 hematology/oncology children fulfilled the eligibility criteria during the study period. The median (range) age was 5.0 (1.0–15.0) years. The majority of the patients, i.e., 5/9 (55.6%), were male. The most common underlying diagnosis was pre-B–cell acute lymphoblastic leukemia (Pre-B-ALL) in 4/9 (44.4%) children. Port-a-catheter was placed in 6/9 (66.3%) children who received ALT for bacteremia. Vancomycin was used in 7/9 (77.8%) children for ALT. All patients, i.e., 9/9 (100%), received systemic antibiotics along with ALT. The median (IQR) dwell time was 48 h (24 h). The median (IQR) days of ALT was 4.0 (7.0) days. The median (range) length of hospital stay was 15.0 (8.0–38.0) days (Table 1). The most common pathogen isolated was *Staphylococcus non-aureus* in 3/9 (33.3%) cases followed by each case, i.e., 1/9 (11.1%), of *S. aureus*, *Staphylococcus saprophyticus*, *Enterococcus* spp., *Pseudomonas aeruginosa*, *Brevibacterium*, and *Bacillus*. Persistent bacteremia was observed in 2/9 (22.2%) patients, and in 2/9 (22.2%) cases, exit site infection was present. Out of 9 children, 2 (22.2%) had a relapse, and in the remaining 7 (77.8%) children, a catheter was salvaged. None of the patients had a metastatic infection or septic shock. All of them survived (Table 2).

Table 1

Demographic statistics of antibiotic lock therapy (ALT) in hematology/oncology children with bloodstream infections (N = 9).

Variables	n (%)
Age (years)	
Median (IQR)	5.0 (8.0)
Gender	
Male	5 (55.6)
Primary diagnosis	
Pre-B-ALL	4 (44.4)
Nasopharyngeal Carcinoma	1 (11.1)
Medulloblastoma	1 (11.1)
Retinoblastoma	1 (11.1)
Right eye rhabdomyosarcoma	1 (11.1)
Ewing Sarcoma	1 (11.1)
Type of catheter	
Porta catheter	6 (66.3)
PICC Line	3 (33.3)
Use of catheter	
Chemotherapy	9 (100)
Absolute Neutrophil Count at the diagnosis, (mm³)	
Median (IQR)	2869 (3289)
Use of systemic antibiotic	9 (100)
Antibiotics used for lock therapy	
Vancomycin	7 (77.8)
Ciprofloxacin	1 (11.1)
Cloxacillin	1 (11.1)
Dose of each ALT (mg)	
Median (IQR)	7.5 (2.5)
Volume of each ALT (ml)	
Median (IQR)	3.0 (0.5)
Dwell time of each ALT(hour)	
Median (IQR)	48 (24)
No of positive blood cultures in the current episode	
Median (IQR)	1.0 (1.0)
Days of Treatment(days)	
Median (IQR)	
Systemic Antibiotic	10.0 (8.0)
ALT	4.0 (7.0)
Number of doses of ALT	
Median (IQR)	3.0 (3.0)
Length of hospital stay (days)	
Median (IQR)	15.0 (11.0)

PICC: Peripherally Inserted Central Catheter; ALT: Antibiotic Lock Therapy.

4. Discussion

In the current review, two thirds of the catheters were salvaged with the use of ALT. One fifth of the patients developed persistent bacteremia requiring removal of the catheter. Cases of catheter salvage included *S. aureus* as well as *P. aeruginosa* for which the current IDSA guidelines recommend removal. These results are comparable with those reported in previous studies conducted in Children's Hospital of Michigan/Wayne State University, in a larger randomized, blinded, multicenter trial from Belgium and from studies conducted in India [12–15]. We observed that the most common pathogen isolated in our study was *Staphylococcus non-aureus*. Further identification of the species was not reported. This is the most common pathogen of bacteremia and reinfection related to central venous carriage (CVC) in studies conducted in other countries as well. This trend is probably because the major microbial flora of the skin comprises staphylococci [16–18]. The organisms present in the skin migrate from the insertion site into the cutaneous catheter tract, thereby resulting in colonization of the tip of the catheter and formation of biofilms [17,19,20]. In several studies, the outcome of ALT is generally better in the less virulent organisms (coagulase-negative staphylococci and enterococci) than the gram-negative organisms and yeast [21]. In our study, the catheter was salvaged with ALT in patients infected with *P. aeruginosa*.

Table 2

Clinical characteristics and outcome of patients treated with antibiotic lock therapy (ALT) for catheter-associated bacteremia.

S. No.	Age/sex	Organism isolated	Type of catheter	ANC (mm ³)	Name of ALT	Dose of ALT (mg)	Dwell time (hours)	No. of ALT doses	Days of ALT	Persistent bacteremia	Catheter salvage	Relapse
1	5 yr/M	<i>Pseudomonas aeruginosa</i>	Port-a-catheter	1915	Ciprofloxacin	0.6	48	5	10	No	Yes	No
2	5 yr/F	<i>Staphylococcus aureus</i>	Port-a-catheter	2869	Cloxacillin	300.0	48	4	8	No	Yes	Yes
3	2 yr/F	<i>Staphylococcus non-aureus</i> sp.	Port-a-catheter	3542	Vancomycin	7.5	24	1	1	No	Yes	No
4	7 yr/M	<i>Staphylococcus non-aureus</i> sp.	PICC line	5464	Vancomycin	7.5	48	1	1	No	Yes	No
5	2 yr/F	<i>Staphylococcus saprophyticus</i>	Port-a-catheter	1890	Vancomycin	7.5	48	4	8	No	Yes	Yes
6	1 yr/M	<i>Enterococcus</i> species	Port-a-catheter	7724	Vancomycin	7.5	48	2	4	No	Yes	No
7	4 yr/F	<i>Brevibacterium</i>	Port-a-catheter	539	Vancomycin	7.5	48	3	7	No	Yes	No
8	12 yr/M	<i>Staphylococcus non-aureus</i> sp.	PICC line	3060	Vancomycin	5.0	24	3	3	Yes	No	No
9	15 yr/M	<i>Bacillus</i>	PICC line	245	Vancomycin	5.0	24	1	1	Yes	No	No

Ti date, literature has not shown any association between catheter removal, type of catheter, neutropenia, and the pathogen isolated [14]. In this study, we observed that the catheter was removed in one of the two severely neutropenic patients and the type of catheter was peripherally inserted central catheter (PICC). Our study showed a high relapse rate of 28.6% compared to those reported in other studies, where the rates were 6.08% and 14.28% [14,22]. An attributing factor could be that one of the two patients had a *S. aureus* infection, for which IDSA guidelines do not recommend ALT. Hence, if we can recognize the risks of undesirable outcomes and eliminate them, then we might be able to further increase the catheter salvage rate.

There was no complication or death noted in the present study despite this being an immunocompromised population. None of the patients developed septic shock or metastatic infection. In a study conducted by Poole, C.V. et al., the rate of serious complications in ALT used for dialysis-catheter-related bacteremia was 7.3% [23].

To the best of our knowledge, this is the first study reporting the outcome of ALT in Pakistan. However, the small sample and retrospective single-centered nature of our study are the major limitations. Therefore, there is a need for sufficiently powered studies to conclusively demonstrate the role of ALT in CRBSI in children as well as in adults.

5. Conclusion

In our experience, in almost two thirds of the cases, the catheter was salvaged, but disappointingly, relapse rates were high when the infection was due to *Staphylococcus* spp. Although this is a small study, our results show that ALT can be a potential safe adjunctive/alternative strategy to treat CRBSI. However, we need larger prospective studies conducted in multiple tertiary healthcare centers to test the safety and efficacy of ALT to develop specific ALT recommendations and guidelines particularly in children.

Conflict of interest

All the authors declare that we have no conflict of interest, whether financial or otherwise.

Declaration of interest

None.

Ethical statement

The study was exempted from Ethical Review Committee of The Aga Khan University Hospital (ERC Ref # 5278-Ped-ERC-18). There are no identifiers of the participants in the manuscript.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

We would like to acknowledge Miss Ale Zehra, pharmacist at Aga Khan University hospital for providing us the data of children who received antibiotic lock therapy.

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