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The implication of intestinal bacterial translocation in central line associated blood stream infections in the pediatric population☆

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ABSTRACT

Introduction: Bacterial intestinal translocation plays an important role in neonatal sepsis. We aimed to elucidate the importance of such translocation in causing central line associated blood stream infection (CLABSI) in patients undergoing gastrointestinal surgery (GIS).
Methods: Using a database of pediatric patients with CLABSI, patients were divided into those who had a GI-surgery (where intestines were opened), those who had a non-GI-surgery (NGIS; all other types of surgery) and those who had no surgery (NS). Data regarding type of organisms isolated on culture, their resistance patterns, clearance of CLABSI, type of antibiotic therapy and patient demographics were collected.
Results: 117 CLABSIs were identified between 2011 and 2018. 26 patients had GIS, 22 had NGIS and 69 had NS. NS patients were younger. 80% of GIS and NGIS patients had a central line at the time of surgery. Coagulase-negative staphylococcus (CoNS) was the most common organism isolated (32%). CoNS was more common in GIS compared to NGIS and NS (58% vs. 9% vs. 29% respectively, $p = 0.04$). There were no differences in the time to resolution of bacteremia, mortality rates or need to remove the central line.
Conclusions: This information should help inform efforts for prevention of CLABSIs in patients undergoing GI surgery with central lines present.
Level of evidence: III

Central venous catheters (CVCs) are an integral part of health care used to provide systemic access for medications and total parenteral nutrition. There are several types of CVCs, namely tunneled, nontunneled, peripherally inserted (PICC), umbilical venous catheters, or completely implanted catheters, such as portacaths. Several complications of CVC exist related to their insertion and use.

A particularly morbid complication of a CVC is a central line-associated bloodstream infection (CLABSI). According to the Center for Disease Control a CLABSI is defined as a laboratory-confirmed bloodstream infection that develops within 48 h of line placement, or thereafter, and is not related to an infection at another site [1]. It is a much broader term than a catheter related blood stream infection which focuses on the catheter as the infection source and requires specific laboratory tests to confirm [2]. The rate of CLABSI varies according to device type and underlying medical problem. In children, reported CLABSI rates range from 0.2 to 11 episodes per 1000 catheter days. The presence of a CLABSI increases patient hospital stay; rates of deep vein thrombosis, endocarditis, and sepsis; delay in discharge; hospitalization cost; and in rare cases death [3,4]. Thus, prevention of CLABSI and mitigating the risk factors for its development are of great importance.

Evidence-based guidelines have continued to reduce the incidence of CLABSI by targeting CVC maintenance and aseptic care. Despite these efforts, certain comorbid conditions place patients with CVC at high risk for the development of CLABSI. For example, oncology patients administered chemotherapy with associated gastrointestinal toxicity develop a higher rate of CLABSI despite adequate central line care. This increased risk of CLABSI in patients with gastrointestinal mucosal disruption has led the Centers for Disease Control to coin a novel term of mucosal barrier injury-associated laboratory-confirmed bloodstream infection (MBI-LCBI) [5,6].

MBI-LCBI is thought to occur when the gastrointestinal tract mucosa is damaged allowing for bacterial translocation. This suspected phenomenon involves a mucosal breach which allows bacteria to migrate into the regional lymphatic system and eventually infiltrate the blood stream [7]. It has been hypothesized that any breach to the intestinal

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mucosa can produce bacterial translocation resulting in a CLABSI in those cases where a CVC is present [8]. While medication toxicity or pathologic intestinal conditions like necrotizing enterocolitis and short gut syndrome have been studied as sources of bacterial translocation and potential risks of CLABSI, there are few studies that have explored the potential impact of pediatric gastrointestinal surgery on the development of CLABSIs [9]. We hypothesize that pediatric patients undergoing gastrointestinal surgery would be at greater risk for the development of CLASBIs. We performed a retrospective study to analyze the characteristics of CLABSIs that have occurred after gastrointestinal surgery, in contrast to CLABSIs related to nongastrointestinal surgery or no surgery in a pediatric population.

1. Methods

Following approval by the Institutional Review Board, a retrospective review was done on all pediatric surgical patients who were identified with a CLABSI while hospitalized from 2011 to 2018 at a tertiary-care pediatric hospital. CLABSIs were defined as a laboratory-confirmed bloodstream infection that developed beyond 48 h from the time of line placement and were not related to an infection at another site. Patients were retrospectively identified within an infection-control, institutional database of patients who developed a CLABSI while receiving inpatient care. Patients on surgical floors, neonatal intensive care units and pediatric intensive care units were included.

Variables of interest included demographic information, type of line placement (tunneled, nontunneled, umbilical venous catheter, PICC), time from surgery to CLABSI, presence of central venous access at surgery, organisms cultured, type of anti-infective therapy employed, resistance patterns, duration of therapy, time to CLABSI resolution, central line removal, and mortality. Time from surgery to CLABSI was the number of days from the surgical procedure to the first positive blood culture. Two positive blood cultures were used to confirm CLABSI, along with physician judgment that bacteremia was not secondary to another infectious process. Organisms cultured were determined by the report from the first positive blood sample. Type of therapy was the initial therapy started after the first positive blood culture. Resistance patterns were determined by microbiology reports. Duration of therapy was the number of days from start to end of therapy. If the antibiotic regimen was changed, the days of subsequent therapy were included. Time to CLABSI resolution was the total number of days from first positive to first negative blood culture.

The gastrointestinal surgery (GIS) cohort was defined as patients who developed a CLABSI within 30-days following a surgical procedure in which bowel was transected or entered during the course of surgery. Surgeries included bowel resection, intestinal anastomosis, ostomy formation, and ostomy takedown. The nongastrointestinal surgery (NGIS) cohort was defined as patients who developed a CLABSI within 30-days following a surgical procedure in which intestine was not entered. The nonsurgical cohort (NS) was defined as patients who developed a CLABSI with no surgical procedure during the index hospital stay.

All surgical procedures, including tunneled, and nontunneled central line placements, were conducted in an operative suite with full sterile precautions. Umbilical venous catheters and PICCs were placed at the bedside or by interventional radiology within their operative suite.

These variables were entered into Indiana University REDCap™ for analysis. Statistical analysis was performed using R-software, utilizing Kruskal–Wallis tests across groups for continuous variables. Fisher's exact tests were utilized for dichotomous variables. P-values less than 0.05 were considered statistically significant. Numerical values were reported with continuous variables represented with a median and interquartile range (IQR) and dichotomous variables were represented as percentages.

2. Results

During the study time period of 2011 to 2018, 120 CLABSIs were identified within the database. Three cases were omitted owing to repeat records. Table 1 illustrates the descriptive information of number, age at time of CLABSI, gender, time from surgery to development of a CLABSI, and percent of patients within the GIS, NGIS and NS groups. Age among the groups were statistically different ($p < 0.001$) while gender, time from surgery to CLABSI, and central venous access present at surgery were not. The most common gastrointestinal surgery performed was a bowel resection (54%). 31% of patients had a bowel perforation prior to surgery (Table 2).

Regarding central line type, Table 3 describes the significant differences of central line placement across groups. Umbilical venous catheters and nontunneled lines were more common among the no surgery group ($p = 0.01$). Most patients had a PICC (45.8%) followed by tunneled (30.5%) and nontunneled/umbilical venous catheters (23.7%).

Table 4 describes CLABSI organisms and therapy among groups. Coagulase-negative staphylococcus (CoNS) was the most common organism isolated (32%). CoNS was more common in GIS (58%) compared to NGIS (9%) and NS (29%) groups ($p = 0.04$) while other organisms displayed no definite distribution patterns among groups.

Type of therapy across groups was significantly different among the groups, (Table 5, $p = 0.02$) with piperacillin-tazobactam used more frequently within GIS patients ($p = 0.01$) and gentamicin among NS patients ($p = 0.04$). The most frequently used therapy was vancomycin (73.5%). While there was therapy resistance (Penicillin, Clindamycin, Gentamicin, Oxacillin, Vancomycin), there were no significant patterns of resistance between groups.

96% of patients received perioperative antibiotics in the GIS cohort (25/26). There were no differences with incidence of CoNS on culture with type of perioperative antibiotic administered — ampicillin, cefazolin, cefoxitin, cefepime vs. cefotaxime for GIS [$p = 0.56$]. The incidences of other organisms were too low to detect meaningful differences.

Regarding CLABSI management and mortality, there were no significant differences in duration of antibiotic therapy, time to resolution of CLABSI, central line removal, or mortality (Table 6). There were no deaths among the patients having GIS and an associated CLABSI.

3. Discussion

While there are several studies that analyze CLABSI prevention and describe bacterial translocation as a risk factor, there are none to our knowledge that have investigated the impact of gastrointestinal surgery on CLABSI occurrence in a pediatric population. Major findings of our study include that CoNS CLABSI was more common in GIS group when compared to NGIS and NS groups. There were no differences among the three groups in the incidence of other organisms attributed to a CLABSI, antibiotic resistance patterns, time to resolution of bacteremia, mortality rates, or need to remove the central line.

Pediatric gut microbiota vary based on several factors such as age, medical conditions, diet, and method of delivery. In one study CoNS

Table 1
Descriptive information regarding patient groups.

	GI Surgery	Non-GI Surgery	No Surgery	P values
N (total number of CLABSIs)	26	22	69	
Age (median years [IQR])	2 [0.9–3.8]	3 [1.1–9.3]	0.7 [0.4–1.7]	<**0.001**
Sex (% male)	46	18	41	0.11
Time from surgery to CLABSI (median days [IQR])	15.5 [12–20.8]	11.5 [8–22]		0.28
Central venous access present at the time of surgery (%)	81	100		0.68

Table 2
Procedure type for gastrointestinal surgery group.

	Percentage %
Bowel Perforation	31
Bowel Resection	54
Bowel Anastomosis	46
Ostomy Formation	38
Ostomy Takedown	19

was implicated as an early gut colonizer, as 99% of pediatric gut flora studied were colonized with CoNS after day three of life [10]. Within western developed countries, CoNS has also been identified as the most common cause of pediatric CLABSIs [11]. Our data are unique in that they demonstrate a higher incidence of CoNS among CLABSIs in patients undergoing gastrointestinal surgery when compared against the NGIS and NS groups. Though contamination of a central catheter by CoNS is often thought to occur from a skin flora source, gastrointestinal translocation following GI surgery could be another reason for this preponderance of CoNS in CLABSIs within this surgical group.

While our GIS patients demonstrate an elevated prevalence of CoNS CLABSI, these data do not definitively identify the origin of the bacteria. CoNS has been identified as a skin flora colonizer, with *S. epidermis* being a frequent infiltrator and biofilm producer of indwelling medical devices. However, a recent study discovered that a majority of cancer patients with bacteremia had CoNS organisms that matched their mucosal rather than skin flora. CoNS has also been shown by genotyping to be a component of the intestinal mucosal flora which is responsible for late onset neonatal sepsis [12]. Furthermore, these results corroborate prior studies that analyzed late onset septicemia in premature infants with central venous access for antibiotic and parenteral nutrition administration. In this population, they determined that the rectal CoNS strains from patients undergoing gastrointestinal surgery matched the blood isolates of the respective CLABSIs [13]. CoNS intestinal colonization has been associated with decreased intestinal integrity in conditions such as necrotizing enterocolitis and short gut syndrome [14,15]. Extrapolating the results of these prior studies, there is the likely possibility that in our GIS patient population, CoNS CLABSI arose from surgically-induced bacterial translocation from the gastrointestinal tract.

Regarding medical management, there were no differences with respect to incidence of other organisms, antibiotic resistance patterns, time to resolution of bacteremia, mortality rates, or need to remove the central line between the three groups. Our GIS CLABSI mortality rate (0%) corroborates with the rarity expressed in prior studies [16,17].

One of the best solutions to tackle CLABSI has been central line bundles, which are evidence-based interventions that standardize the protocols for central line care beyond initial catheter placement. Prior research has demonstrated central line bundle effectiveness in a wide array of clinical settings, including pediatrics [18,19]. Based on our data and inference of translocation contributing to CLABSI in patients undergoing gastrointestinal surgery, our study identifies the need for further research to fully determine the possible causality implied. Future research might then inform guidelines for central line care in the postoperative setting that would mitigate the possible impact of CoNS translocation.

Table 3
Type of central line.

	GI Surgery	Non-GI Surgery	No Surgery	P values
Tunneled	9	13	14	0.06
Nontunneled/umbilical venous catheter	2	1	24	**0.01**
Peripherally inserted central catheter	15	8	31	0.67

Table 4
CLABSI organisms among patient groups.

	GI Surgery	Non-GI Surgery	No Surgery	P values
CoNS	15	2	20	**0.04**
Staphylococcus aureus	3	7	13	0.38
MRSA	0	1	2	0.77
Enterococcus faecalis	2	4	8	0.63
Enterococcus cloacae	1	2	3	0.72
Candida albicans	0	3	4	0.18
Candida glabrata	0	0	1	1
E. coli	2	2	9	0.79
Pseudomonas aeruginosa	0	0	4	0.47
Klebsiella pneumoniae	3	2	4	0.57

One proposed solution to mitigate surgical bacterial translocation is the administration of pre- and perioperative probiotics. Probiotics have been purported to decrease the rate of bacterial translocation and increase gut membrane integrity. The mechanism involves the colonization of innocuous bacteria to outcompete harmful ones. Current studies have mixed interpretations about probiotic effectiveness. However, probiotics could be a potential therapy to prevent bacterial translocation of pathologic organisms and further research is required for this potential use [20].

One limitation of our study was the absence of data on total CVC duration prior to infection and lack of comparison to patients with bacteremia without central lines. A previously published, prospective study showed that CVC duration, emergency surgery, and male gender were risk factors for catheter related blood stream infections [21]. Additionally, the lack of data regarding the absolute incidence of bacteremia or CLABSI among the three defined groups illustrates a clear limitation of this study through its use of retrospective data of only those patients with a defined CLABSI. This study, thus, cannot conclude the absolute frequencies of CLABSI in similar populations or of the true prevalence of the noted organisms on the development of CLABSI.

In this study, nonsurgical patients with CLABSIs had a greater incidence of nontunneled lines and umbilical venous catheters. One explanation could be the younger age of the no-surgery (NS) patients and the type of catheters used in this nonoperative group. Nontunneled lines are frequently used for short durations in care. They are a preferred mode of access when other routes fail, such as peripheral intravenous lines. Umbilical venous catheters are the more prevalent central line option in newborn infants frequently requiring nutrition or antibiotics. Evidence has suggested that they are more advantageous at reducing the frequency of venipunctures and subcutaneous extravasation within this population [22]. We did not find any differences in incidence of CoNS with the type of central line for any of the groups (data not shown).

4. Conclusion

Our results demonstrate that there is a statistically significant connection between CoNS CLABSI and patients undergoing gastrointestinal

Table 5
Type of therapy and resistance among patient groups.

	GI Surgery	Non-GI Surgery	No Surgery	P values
Type of therapy (*n*)				
Vancomycin	21	13	52	0.78
Cefepime	4	9	24	0.3
Piperacillin-Tazobactam	15	3	13	**0.01**
Gentamicin	0	0	10	**0.04**
Fluconazole	7	5	19	1
Resistance (%)				
Penicillin	94	80	78	0.93
Clindamycin	60	22	65	0.47
Gentamycin	17	6	9	0.6
Oxacillin	67	38	59	0.79
Vancomycin	0	0	0	1

Table 6
Clinical information among patient groups.

	GI Surgery	Non-GI Surgery	No Surgery	P values
Duration of therapy (median days[IRQ])	11 [10–16.5]	12 [10.3–15.5]	13 [7–16]	0.86
Time to resolution of CLABSI (median days [IQR])	3 [2–4]	2 [1–3]	3 [1–5]	0.68
Central line removed (%)	54	45	41	0.52
Death (%)	0	5	16	0.07

surgery among a pediatric population. Future directions for this work would be to definitively test the supposition for translocation-associated CLABSIs in patients undergoing gastrointestinal surgery with central catheters. Such work should standardize the definition of such variants of CLABSI [23], identify what preventive measures could be developed, and determine how these therapies would decrease CLABSI incidence among surgical patients.

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