NIH Public Access
Author Manuscript
J Pediatr Surg. Author manuscript; available in PMC 2014 September 01.

Published in final edited form as:
J Pediatr Surg. 2013 September ; 48(9): 1936–1940. doi:10.1016/j.jpedsurg.2013.05.065.

Profound systemic inflammatory response syndrome following non-emergent intestinal surgery in children☆

Bhani K. Chawla and **Daniel H. Teitelbaum***
Department of Surgery, Section of Pediatric Surgery, University of Michigan, Ann Arbor, MI 48109-0245, USA

Abstract

Purpose—Systemic inflammatory response syndrome (SIRS) is an uncommon but severe complication in surgical patients. While SIRS is well known, it is poorly described in the pediatric population. The goal of this study was to describe the incidence of profound SIRS following non-emergent intestinal surgery in children and to identify potential risk factors.

Methods—A retrospective review was conducted for patients 0–19 years of age following intestinal surgery and/or lysis of adhesions from 01/01/1999-02/28/2012. Children were excluded for preoperative instability or frank bowel perforation. Patients were then placed in a post-operative SIRS or non-SIRS group as defined by the 2005 International Pediatric Sepsis Consensus Conference Guidelines (6. B. Goldstein, B. Giroir, A. Randolph, and Sepsis International Consensus Conference on Pediatric, ‘International Pediatric Sepsis Consensus Conference: Definitions for Sepsis and Organ Dysfunction in Pediatrics’, Pediatr Crit Care Med, 6 (2005), 2–8.).

Results—SIRS was identified in 17 of the 381 patients. Logistic regression analysis was performed and showed heart disease, kidney disease, PN dependence, and intestinal obstruction to be predictive of post-operative SIRS.

Conclusion—This study represents one of the first reports to identify a previously poorly described process of significant SIRS after intestinal surgery in children. Both systemic organ failure and intestinal dysfunction are strong risk factors for post-operative SIRS in children. Potentially, these pre-existing conditions may lead to disruption of normal intestinal flora or barrier function, which in turn may predispose these children for dramatic SIRS after intestinal surgery. Understanding how these factors lead to SIRS will be critical to developing prevention strategies.

Keywords

Systemic inflammatory response syndrome; SIRS; Intestinal surgery; Parenteral nutrition

Intense systemic inflammatory response syndrome (SIRS) following non-intestinal surgeries has been documented in the literature predominately in adults who are otherwise healthy patients [1–3]. This has been characterized in children, but to a far lesser degree [4]. Importantly, significant SIRS following bowel resections or lysis of adhesions, in the absence of infection, bowel perforation or necrosis has not been described in the literature. The etiology of these SIRS events also remains poorly understood. Sudden, inexplicable

☆Disclosures: The authors have no relevant disclosures.

*Corresponding author. Tel.: +1 734 936 8464; fax: +1 734 936 9784, dttlbm@umich.edu (D.H. Teitelbaum).

instability or shock following what should be a routine surgery can lead to lasting morbidity or even death. Integral to treating shock is addressing the underlying source. Thus, identifying risks and causative factors may allow physicians to better optimize patients preoperatively, manage patients perioperatively and possibly prevent this detrimental outcome from occurring.

Isolated cases of profound postoperative stress responses or SIRS following intestinal resection or adhesiolysis have been anecdotally noted by pediatric surgeons at the C.S. Mott Children's Hospital. However, it is not clear how frequently such an event occurs in children. The goals of this study include attempting to determine overall incidence of postoperative SIRS by examining all infants and children undergoing non-emergent intestinal resection or adhesiolysis over the past 13 years as well as identifying potential contributing factors.

1. Methods

Approval for this study was obtained through the institutional IRB prior to any data collection (HUM00056147). Patients between the ages of 0 and 19 years old who underwent intestinal (small and/or large bowel) surgery or lysis of adhesions from 01/01/1999-02/28/2012 were identified using a search of billed procedures for all pediatric surgeons at our institution within the electronic medical charting system. Specifically, the terms include: "entrectomy", "colectomy", "bowel resection", "lysis of adhesions", "enterolysis" and "adhesiolysis." The patients of interest from this list were children that were not already predisposed towards postoperative instability. Thus, patients that were significantly unstable preoperatively or were being operated on for frank bowel perforation or intestinal necrosis were excluded. A retrospective review was then conducted identifying patients that postoperatively exhibited a severe Systemic Inflammatory Response Syndrome (SIRS) or shock (septic or septic shock-like syndrome). The definition of severe sepsis and septic shock were taken from the landmark paper "International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics" [5]. However, as not all patients in a state of significant SIRS had identifiable sources of infection, instead of using the terms "severe sepsis" or "septic shock" to define the post-operative course of children within the study group, the terms of "severe SIRS" and "SIRS related shock" are used instead. These terms indicate states of inflammation identical to severe sepsis and septic shock, but in the absence of defined infection, similar to what has been coined already in the adult population [6]. As stated above, patients with obvious intra-abdominal sources of post-operative severe sepsis or septic shock such as frank perforation and luminal leaks were also excluded. Children that met these criteria made up the study group (SIRS group). The remaining children were placed in the control group (Non-SIRS group). The two groups were then compared using univariate analysis (Fisher's Exact test) to identify potential risk factors of a significant post-operative SIRS. Statistical significance was defined on an alpha value of 0.05. A secondary logistic regression analysis was also performed (SPSS version 19.0) on key risk factors identified by univariate analysis, in order to exclude confounding covariates. These latter results are reported as the beta coefficient and P value.

Gender, age, length of stay, type of surgery, indication for surgery, past medical history, immunosuppression, past surgical history, and route of nutrition were the major categories compared between the two groups. The types of surgical procedures were divided into small bowel surgery, colonic surgery, and lysis of adhesions only. Operations included intestinal resections, anastomoses, enteroplasties, and/or otomy manipulation. These surgeries were then placed into their respective category based on location. Surgical indications were separated into categories of bowel atresia, adhesive or strictured small bowel obstruction, adhesive or strictured colonic obstruction, entercutaneous fistula, gastrointestinal bleed, intussusception, mass, unwanted stoma, imperforate anus, short gut syndrome, inflammatory bowel disease and other. The "other" category grouped the following indications together: meconium ileus, dysmotility, abdominal pain, blunt trauma causing mesenteric disruption, gastroesophageal reflux disease, incarcerated congenital diaphragmatic hernia, choledochal cyst, cloacal exstrophy, and malrotation. Within the past medical history category, included variables were history of chronic organ dysfunction such as heart disease (congenital heart defects), lung disease, mental disorders, kidney disease, or liver disease, as well as history of prematurity and/or malignancy. Intestinal derangements were also analyzed, and included: history of inflammatory bowel disease, dysmotility, short gut syndrome and/or history of infectious bowel disease. Infectious bowel disease indicated a history of *Clostridium difficile* or enterocolitis. Past surgical history categories included previous bowel surgery, other abdominal surgeries, heart surgery, and kidney or liver transplants. Mode of nutrition was categorized by enteral intake and use of parenteral nutrition (PN). Enteral intake was defined as any type of oral or enteral consumption or nutrition via tube feeds, including clear liquids. Patients were then demarcated into two categories based on no enteral intake for a week or more. Similarly, PN was defined as any intravenous nutrition, whether supplied peripherally or through a central line. Patients were then separated into two categories: those that were PN dependent and those that were not.

2. Results

Four hundred sixty-four patients were identified in the initial review. Patients were immediately excluded (N = 83) for a lack of data or based on the defined exclusion criteria (Methods). Of these, 17 children were found to have severe SIRS post-operatively and comprised the SIRS group. The non-SIRS group included the remaining 364 patients. Age, gender and mean hospital stay for each group is detailed in Table 1. Of the SIRS group 9/17 (53%) patients were less than 6 months of age compared with 155/364 (43%) in the non-SIRS group ($P = 0.457$).

Six of the 17 patients within the SIRS group underwent further surgical re-exploration. These additional surgeries were not included in the comparison of surgical indication between the two groups; however, an intra-abdominal source of the SIRS (e.g., necrotic bowel or perforation) was not identified. Because all of these patients were unstable preoperatively and were already included in the SIRS group, these operations were automatically excluded from the study. Comparison of types of procedures and different indications for surgery are detailed in Tables 2 and 3. Some patients had surgery for more than one indication. Receiving an operation for a small bowel obstruction was significantly more frequent in the SIRS group (11/17, 65%) than the non-SIRS group (106/364, 29%; $P = 0.005$). Similarly when total number of intestinal obstructions were compared between the two groups, there were a significantly higher number in the SIRS group (13/17, 77%) compared to the non-SIRS group (178/364, 49%; $P = 0.044$). Total intestinal obstructions combined the categories of small bowel obstruction, colonic obstruction, atresia and intussusception. The operative indication of obstruction was also significant by logistic regression ($\beta = 1.374$, $P = 0.045$).

In the SIRS group, while no patient was unstable prior to surgery, 2 children (12%) became unstable intraoperatively, 11 (65%) had severe SIRS or shock within the first postoperative day, and 4 (24%) developed a significant inflammatory response within 2 days of surgery. Only 35% (6/17) of SIRS patients had identified sources of sepsis, and no SIRS patient had post-operative necrotic bowel or frank leakage of enteric content as an identified source of SIRS. One patient, however, that was unstable within hours after surgery and initially did not have frank necrosis on re-exploration the night of surgery, developed global intestinal ischemia bowel 2 days postoperatively secondary to profound shock and vasopressor dependence. The majority of this child's small bowel was thus resected. In addition, 16 patients (94%), required care in the intensive care unit, 12(71%) required re-intubation, 10 (59%) were dependent on one or more intravenous pressors, 6 (35%) underwent re-exploration of the abdomen to examine for source of the SIRS, 3 patients (18%) developed acute renal failure and a total of 3 patients (18%) died following surgery. One patient died within a few hours of surgery, another passed away 2 days after the index operation. Both of these patients died from profound shock after undergoing surgery for bowel obstruction. The 3rd patient's death occurred a month after the index operation for a takedown of an enterocutaneous fistula. He had cardiopulmonary arrest of unclear etiology twice prior to passing away; the first two days postoperatively and then again two weeks later. He progressively developed multiorgan failure and care was withdrawn. A total of 19 patients within the control group had died by the completion of data collection on February of 2012. While SIRS patients had a higher mortality rate (3-fold), the difference was not significantly different between the two groups: 3/17(18%) vs. 19/364 (5%) ($P = 0.067$).

Of medical conditions evaluated, history of heart disease, liver disease, kidney disease, prematurity, and infectious bowel disease were all statistically significantly more common in those children developing SIRS (via univariate analysis). Other disease states evaluated were not statistically significant (Table 4). None of the past surgical history variables were significantly different between the two groups. Use of PN at the time of the abdominal surgery was strikingly different between the two groups with 12/17 (71%) in the SIRS group dependent on PN compared to 131/364 (36%) in the non-SIRS group ($P = 0.008$). Interestingly, there was also a major difference in lack of enteral nutrient intake (>7 days) between the SIRS and control groups; 5/17(29%) versus 33/364(10%) ($P = 0.017$). However, this information was unclear for 30 patients. Thus in the final statistic, only patients that were definitively lacking enteral consumption for a week or more were included in the analysis. Based on these findings a secondary analysis of the data was performed using logistic regression of the positive findings from univariate analysis. Statistical significance was identified for use of TPN ($\beta = 1.270$, $P = 0.047$), history of heart disease ($\beta = 1.673$, $P = 0.023$), and history of kidney disease ($\beta = 1.783$, $P = 0.041$) as predictive for the development of post-operative SIRS.

3. Discussion

Systemic inflammatory response syndrome (SIRS) has been recognized since the 1980s as a stress response associated with tachycardia, tachypnea, fever and leukocytosis. This term entered common use after the 1992 ACCP/SCCM Consensus Conference. This syndrome groups together the clinical signs that result from systemic activation of the innate immune system, without consideration of the cause. Multiple initializing triggers have been identified: infection, trauma, surgery, among other stressors [7]. Unexpected intense SIRS response following routine surgeries have been noted anecdotally as well as in the literature. However, how to account for the severity of response when significant post-operative SIRS does occur remains poorly understood. Why do some patients experience a profound state of inflammation following surgery when other patients recover without difficulty? This study aimed to examine this question further.

The pediatric population is especially of interest as the innate immune system is in varying stages of development depending on prematurity and age. In this study, age was not significantly different between the two groups. However, there was a significantly higher rate of prematurity in the SIRS group by univariate analysis; but this was not predictive on logistic regression.

One observation that has been well documented in regards to explaining the development of severe SIRS is that patients with pre-existing illness have worse outcomes [6]. The innate immune system may be already primed towards an exaggerated response following stress. This study further corroborates this fact. The rates of history of chronic heart disease, liver disease, and kidney disease were considerably higher in the SIRS group; and heart disease and kidney disease were predictive by logistic regression as well.

The gut has been implicated as an instigator of systemic inflammation [8–10]. Breakdown of epithelial barrier integrity or depression of the intestinal immune system has been shown to occur due to direct insult as well as distant stressors [10–12]. In the present study in addition to chronic, extra-intestinal illnesses, a lack of enteral nutrition, presence of intestinal obstruction, and history of infectious bowel disease were all significantly higher in the SIRS group. Obstruction remained significant by logistic regression. Interestingly, TPN dependence was also significantly higher in the SIRS group. In the literature, TPN has been shown to be a risk factor for systemic infections in patients [13–15]. Animal studies indicate that TPN predisposes to a hyperactive response to infection [8,9,16]. The findings of our study suggest that TPN and/or gut disuse may prime the body for a hyperactive inflammatory response in a more general sense than just to infection as in this case the response to a different type of stress, intestinal surgery. The potential source of this systemic response could well be production of pro-inflammatory cytokines induced by the deranged intestinal physiologic condition found in children described in this report.

Along with direct intestinal derangement, bacterial translocation and alterations of the intestinal microbiome may be other potential causes of severe post-operative SIRS, given the significant difference between the two groups in use of TPN/gut disuse, presence of obstruction, and history of infectious bowel disease. Animal studies have shown that TPN and lack of enteral nutrition cause local increased gut inflammation and breakdown of gut barrier function which can increase bacterial translocation [9–11,16]. Obstruction and intestinal infection also affect the intestinal microbiome [17]. In the literature, changes in the intestinal microbiome predispose patients to significant inflammation, again, by breakdown of gut barrier function [18,19]. In conjunction, these findings indicate that maintenance of local intestinal immune system integrity has systemic implications.

In conclusion, SIRS post intestinal surgery in children is an important and not previously recognized process with high morbidity and mortality. Continuing to understand the mechanisms and importance of intestinal immunoregulation may lead to future interventions to help to anticipate those children at risk for post-operative SIRS, and potentially to prevent and treat the predisposition of significant SIRS reactions in PN dependent and enteral nutritionally-deficient patients.

References

1. Kerbaul F, Guidon C, Lejeune PJ, et al. Hyperprocalcitonemia is related to noninfectious postoperative severe systemic inflammatory response syndrome associated with cardiovascular dysfunction after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2002; 16:47–53. [PubMed: 11854878]
2. Schalte G, Henzler D, Waning C, et al. Case study of hepatic radiofrequency ablation causing a systemic inflammatory response under total intravenous anesthesia. Korean J Radiol. 2010; 11:640–7. [PubMed: 21076590]
3. Shen P, Wei W, Yang X, et al. The Influence of percutaneous nephrolithotomy on human systemic stress response, SIRS and renal function. Urol Res. 2010; 38:403–8. [PubMed: 20204340]
4. Kozik DJ, Tweddell JS. Characterizing the inflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg. 2006; 81:S2347–54. [PubMed: 16731102]

5. Goldstein B, Giroir B, Randolph A, et al. International Pediatric Sepsis Consensus Conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005; 6:2–8. [PubMed: 15636651]

6. Muckart DJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Definitions of the Systemic Inflammatory Response Syndrome and Allied Disorders in Relation to Critically Injured Patients. Crit Care Med. 1997; 25:1789–95. [PubMed: 9366759]

7. Levy MM, Fink P, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003; 31:1250–6. [PubMed: 12682500]

8. Hagiwara S, Iwasaka H, Shingu C, et al. Effect of enteral versus parenteral nutrition on inflammation and cardiac function in a rat model of endotoxin-induced sepsis. Shock. 2008; 30:280–4. [PubMed: 18197141]

9. Ikeda T, Hiromatsu K, Hotokezaka M, et al. Up-regulation of intestinal toll-like receptors and cytokines expressions change after TPN administration and a lack of enteral feeding. J Surg Res. 2010; 160:244–52. [PubMed: 19524259]

10. Wildhaber BE, Yang H, Spencer AU, et al. Lack of enteral nutrition—effects on the intestinal immune system. J Surg Res. 2005; 123:8–16. [PubMed: 15652945]

11. Feng Y, Ralls MW, Xiao W, et al. Loss of enteral nutrition in a mouse model results in intestinal epithelial barrier dysfunction. Ann N Y Acad Sci. 2012; 1258:71–7. [PubMed: 22731718]

12. Smith JS Jr, Frankenfield DC, Souba WW. Nutrition and metabolism. Greenfield's Surgery Scientific Principles and Practice. 2006; Ch 3:53–75.

13. Danzig LE, Short LJ, Collins K, et al. Bloodstream infections associated with a needleless intravenous infusion system in patients receiving home infusion therapy. JAMA. 1995; 273:1862–4. [PubMed: 7776503]

14. Gramlich L, Kichian K, Pinilla J, et al. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition. 2004; 20:843–8. [PubMed: 15474870]

15. Marra AR, Opilla M, Edmond MB, et al. Epidemiology of bloodstream infections in patients receiving long-term total parenteral nutrition. J Clin Gastroenterol. 2007; 41:19–28. [PubMed: 17198060]

16. Feng Y, Teitelbaum DH. Epidermal growth factor/TNF-alpha transactivation modulates epithelial cell proliferation and apoptosis in a mouse model of parenteral Nutrition'. Am J Physiol Gastrointest Liver Physiol. 2012; 302(2):G236–49. [PubMed: 22075779]

17. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. World J Gastroenterol. 2010; 16:2978–90. [PubMed: 20572300]

18. Festi D, Schiumerini R, Birtolo C, et al. Gut microbiota and its pathophysiology in disease paradigms. Dig Dis. 2011; 29:518–24. [PubMed: 22179206]

19. Goto Y, Kiyono H. Epithelial barrier: an interface for the cross-communication between gut flora and immune system. Immunol Rev. 2012; 245:147–63. [PubMed: 22168418]

Table 1

Demographic comparison of SIRS and non-SIRS patients.

Demographic	SIRS patients n = 17	Non-SIRS patients n = 364
Age at surgery in years (mean ± SD, range)	1.1 ± 7.9 (0–19.4)	5.5 ± 6.7 (0–19.9)
Hospital stay in days (mean ± SC, range)	48.1 ± 41.3 (1–135)	27.8 ± 44.6 (0–345)
Male gender[a]	9 (53%)	211 (58%)

[a] *P* value 0.802 by Fischer's Exact test.

Table 2

Frequency of major surgical indications in SIRS and non-SIRS patients.

Indication	SIRS Patients n = 17[a]	Non-SIRS Patients n = 364[a]	*P* value[2] α = 0.05
Atresia	1 (6%)	36 (10%)	1.000
Small bowel obstruction	11 (65%)	106 (20%)	0.005
Colonic obstruction	2 (12%)	19 (5%)	0.239
Enterocutaneous fistula	1 (6%)	7 (2%)	0.308
GI bleed	0 (0%)	9 (2%)	1.000
Intussusception	0 (0%)	18 (5%)	1.000
Mass	0 (0%)	21 (6%)	0.613
Unwanted stoma	2 (12%)	50 (14%)	1.000
Bowel lengthening for short gut	1 (6%)	4 (1%)	0.205
Inflammatory bowel disease	0 (0%)	19 (5%)	0.383
Other[3]	2 (12%)	84 (23%)	0.381
Total number of obstructions[4,5]	13 (76%)	178 (49%)	0.044

[a]Several patients were operated on for more than one indication, Fisher's Exact test.

Table 3

Frequency of major surgical indications in SIRS and non-SIRS patients.

Indication	SIRS patients n = 17[a]	Non-SIRS patients n = 364[a]	P value[b] α = 0.05
Atresia	1 (6%)	36 (10%)	1.000
Small bowel obstruction	11 (65%)	106 (20%)	0.005
Colonic obstruction	2 (12%)	19 (5%)	0.239
Enterocutaneous fistula	1 (6%)	7 (2%)	0.308
GI bleed	0 (0%)	9 (2%)	1.000
Intussusception	0 (0%)	18 (5%)	1.000
Mass	0 (0%)	21 (6%)	0.613
Unwanted stoma	2 (12%)	50 (14%)	1.000
Bowel lengthening for short gut	1 (6%)	4 (1%)	0.205
Inflammatory bowel disease	0 (0%)	19 (5%)	0.383
Other[c]	2 (12%)	84 (23%)	0.381
Total number of obstructions[d,e]	13 (76%)	178 (49%)	0.044

[a]Several patients were operated on for more than one indication, three in the SIRS group; n = 17 total surgeries is less than the total indications (N = 20); in the control group, n = 364 total surgeries is less than total of indications (N= 373).

[b]Fisher's Exact test.

[c]Other indications include blunt trauma, imperforate anus, meconium ileus, gastro esophageal reflux (GERD), congenital diaphragmatic hernia, biliary atresia, choledochal cyst, cloacal exstrophy, malrotation, abdominal pain.

[d]Includes any obstruction in the combined categories of atresia, small bowel obstruction, colonic obstruction and intussusception.

[e]One patient in the SIRs group was operated on for both colonic obstruction and a small bowel volvulus and is thus counted only once in the total obstruction category.

Table 4

Comparison of pre-existing conditions between SIRS and non-SIRS patients.

Variable	**SIRS patients n = 17**[a]	**Non-SIRS patients n = 364**[a]	**P value**[a] **α = 0.05**
Statistically significant			
Heart disease	4 (24%)	27 (7%)	0.36
Kidney disease	3 (18%)	11 (3%)	0.020
Liver disease	5 (29%)	34 (9%)	0.021
Prematurity	10 (59%)	113 (31%)	0.030
History of infectious bowel	8 (47%)	70 (19%)	0.011
Parental nutrition	12 (71%)	131 (36%)	0.008
Absence of enteral intake	5 (29%)	33 (9%)	0.019
Not statistically significant			
Lung disease	4 (24%)	82 (23%)	1
Mental disorder	2 (12%)	32 (9%)	0.656
History of malignancy	0 (0%)	15 (4%)	1
History of inflammatory bowel disease	1 (6%)	42 (12%)	0.705
Short-gut syndrome	2 (12%)	23 (6%)	0.308
Cystic Fibrosis	0 (0%)	7 (2%)	1
Hirschsprung disease	1 (6%)	14 (4%)	0.502
Steroid dependence	2 (12%)	57 (16%)	1

[a]Fisher's Exact test.