Journal of Pediatric Surgery 51 (2016) 1022–1025

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Laboratory evaluation for pediatric patients with suspected necrotizing soft tissue infections: A case–control study

Luke R. Putnam [a], Morgan K. Richards [b], Brinkley K. Sandvall [c], Richard A. Hopper [c], John H.T. Waldhausen [b], Matthew T. Harting [a,*]

[a] Department of Pediatric Surgery, Children's Memorial Hermann Hospital, University of Texas McGovern Medical School, Houston, TX, USA
[b] Division of Pediatric Surgery, Seattle Children's Hospital, University of Washington, Seattle, WA, USA
[c] Division of Pediatric Plastic Surgery, Seattle Children's Hospital, University of Washington, Seattle, WA, USA

ARTICLE INFO

Article history:
Received 23 February 2016
Accepted 26 February 2016

Key words:
Necrotizing soft tissue infection
Necrotizing fasciitis
Pediatric infection
Lab risk indicator for necrotizing fasciitis

ABSTRACT

Background/Purpose: Optimal outcomes for necrotizing soft tissue infections (NSTI) depend on rapid diagnosis and management. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is a validated diagnostic tool for adult NSTI, but its value for children remains unknown. We hypothesized that modification of the LRINEC score may increase its diagnostic accuracy for pediatric NSTI.

Methods: We performed a case–control study of pediatric patients (age <18) with NSTI (cases) and patients with severe soft tissue infections prompting surgical consultation (controls). The LRINEC score was calculated for cases and controls and compared to a modified, pediatric LRINEC (P-LRINEC) score. Diagnostic accuracy was analyzed through receiver operating characteristic (ROC) curves.

Results: From 2010 to 2014, 20 cases and 20 controls were identified at two children's hospitals. Median LRINEC score was 3.5 (1–8) for cases and 2 (1–7) for controls ($p = 0.03$). The P-LRINEC was comprised of serum CRP >20 (sensitivity = 95% (95%CI 79–100%)) and serum sodium <135 (specificity = 95% (95%CI 82–100%)). Area under ROC curves was 0.70 (95%CI 0.54–0.87) for the LRINEC score and 0.84 (95%CI 0.72–0.96) for the P-LRINEC score ($p = 0.06$).

Conclusion: The P-LRINEC is a simplified version of the LRINEC score utilizing only CRP and sodium and may provide superior accuracy in predicting pediatric NSTI.

Necrotizing soft tissue infections (NSTI) comprise a spectrum of rare but fulminant infections that lead to widespread necrosis of the subcutaneous tissue and fascia. Recent data suggest mortality rates among adults with NSTI range from 10% to 20% [1–3]. Prompt diagnosis and early, aggressive surgical intervention are the keys to reducing devastating outcomes such as amputation, severe functional limitations, and ultimately death [3–5]. The condition is so rare, with an estimated prevalence of 0.02%–0.03% of all hospitalization causes, that providers have minimal experience with NSTI leading to further delays in diagnosis [1,6]. Such infrequent exposure and limited expertise are magnified in pediatric NSTI [7].

A validated NSTI scoring system called the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was developed in 2004 with routine labs including hemoglobin, white blood cell count, glucose, sodium, creatinine, and C-reactive protein [8]. The scoring system was developed using a predominantly adult cohort of patients and has not been widely reported for use among children with suspected NSTI. Our objective was to determine the utility of the LRINEC scoring system in the pediatric population. We hypothesized that a subset of the laboratory components within the LRINEC scoring system would have stronger predictive value than others and that a modified version of the LRINEC score may increase the accuracy of pediatric NSTI diagnosis.

1. Materials and methods

1.1. Study design and setting

We performed a dual-center, case–control study examining the association between NSTI and the LRINEC score among patients <18 years old. Patient cohorts were selected from Children's Memorial Hermann Hospital, a quaternary, 278-bed children's hospital within the Texas Medical Center in Houston, Texas, and Seattle Children's Hospital, a quaternary, 250-bed children's hospital in Seattle, Washington. Pediatric surgeons, pediatric plastic surgeons, and/or pediatric orthopedic surgeons performed all operations during the study time-period. The STROBE Statement for case–control studies was utilized to guide data reporting [9]. The study was approved by the Institutional Review Boards of both institutions (SCH-15210, HSC-MS-14-0542).

* Corresponding author at: University of Texas McGovern Medical School at Houston, 6431 Fannin Street, MSB 5.220. Tel.: +1 713 500 7300; fax: +1 713 500 7296.
E-mail address: matthew.t.harting@uth.tmc.edu (M.T. Harting).

http://dx.doi.org/10.1016/j.jpedsurg.2016.02.076
0022-3468/

1.2. Case and control identification/definition

Cases of NSTI and controls with severe, soft tissue infections were initially identified using International Classification of Diseases (ICD) codes, 9th revision. The ICD-9 codes for necrotizing fasciitis (728.86), gas gangrene (040.0), and Fournier gangrene (608.83) were used to identify potential cases with NSTI from 2010 to 2014 within both institutions. Inclusion criteria for pediatric NSTI were 1) patients <18 years and 2) documented presence of NSTI in the operative note through keywords such as *necrotizing infection*, *dishwater-like fluid* or *tissue necrosis*, and/or a description of extensive debridement including subcutaneous tissue and muscle with attention to viable circumferential margins. Additionally, NSTI was independently confirmed by two surgeons at each institution. Controls with severe, soft tissue infections and/or abscesses requiring >72 hours of hospitalization were identified using ICD-9 codes 682.1 through 682.9 (cellulitis and abscess of various body areas) during the same 5-year period. Inclusion criteria for controls were 1) patients <18 years, 2) surgical consultation (with or without surgical intervention) during the same inpatient admission, 3) a complete panel of LRINEC laboratory values on admission, and 4) no evidence of NSTI in the consult, progress reports, or operative notes. Controls meeting all inclusion criteria were randomly selected by incidence density sampling.

1.3. Patient characteristics and hospital course details

Clinically important data such as patient demographics, mechanism of injury, presentation signs and symptoms, operative details, laboratory and radiographic findings, microbiology/pathology reports, hospital course, and outcomes were reviewed.

1.4. Statistical analysis

Patient demographics and other categorical data were compared using χ^2 tests, and continuous data were compared with Student's t-test or Mann–Whitney U tests. Continuous variables were converted to categorical variables using Youden's index to determine a cut point with maximum sensitivity and specificity. Univariate logistic regression analysis of each LRINEC lab value was performed, and any variable with a p-value ≤0.2 on univariate analysis was included in the multivariate logistic regression model in a backwards, stepwise fashion to determine variables independently associated with NSTI. Patient age was also included in the multivariate model given its clinical importance.

Based on methods similar to those previously described [8,10], we developed a pediatric LRINEC score (P-LRINEC) by maximizing the area under receiver operating characteristic curves (AUC). Sensitivity, specificity, negative predictive values (NPV), positive predictive values (PPV), and likelihood ratios are reported for the laboratory values included in the LRINEC and P-LRINEC. Stata 13.1 (StataCorp LP, College Station, TX) was used for all statistical analyses.

2. Results

2.1. Patient demographics and presentation

A total of 20 patients with NSTI were identified over the 5-year period, which were compared to 20 non-NSTI patients with severe, soft tissue infections. Median age (range) of NSTI and non-NSTI patients was 5 years (1 month – 17 years) and 6 years (2 months – 17 years, $p = 0.87$). Thirty percent of NSTI patients and 50% of non-NSTI patients were female ($p = 0.20$). Three (15%) NSTI patients and 4 (20%) non-NSTI patients were immunocompromised or were previously diagnosed with a systemic condition such as insulin-dependent diabetes, ulcerative colitis, biliary atresia, or cancer ($p = 0.68$).

The inciting events for both groups, including trauma, animal bites, or instrumentation, were similar overall, although there were more non-NSTI patients in whom no inciting event was identified (25% vs 65%, $p = 0.03$). The primary anatomic sites of infection were similar between groups with the extremities being the most common in both groups (both 60%) followed by the head and neck (20% NSTI, 15% non-NSTI). Median duration of symptoms at the time of presentation for NSTI and non-NSTI patients was 48 h (18–192) and 72 h (24–168), respectively ($p = 0.05$). Erythema was present for all patients; however, only three NSTI patients (15%) versus no non-NSTI patients demonstrated bullae ($p = 0.23$), and no patients in either group demonstrated crepitance.

2.2. Operative details and hospital course

NSTI patients underwent a median of 5 (2–10) operations versus 2 (0–3) operations for non-NSTI patients ($p < 0.01$). Intraoperatively, 8 (40%) patients with NSTI were found to have *dishwater-like fluid*, and necrotic tissue was confirmed in 19 (95%) pathologic specimens. Nine (45%) NSTI patients required at least limited skin excision though only 2 (10%) required skin-grafting. Positive microbiologic tissue cultures were confirmed in 18 (90%) NSTI patients: 8 (44%) Group A streptococcus, 7 (39%) other mono-microbial, and 3 (17%) poly-microbial. Median hospital length of stay was 12.5 days (3–36) and 4 days (3–15) for NSTI and non-NSTI patients, respectively ($p < 0.01$). One (5%) NSTI patient and 2 (10%) non-NSTI patients were readmitted, all because of wound complications. There were no deaths in either group.

2.3. Laboratory results

Median (range) laboratory values for NSTI and non-NSTI patients were similar except for CRP, which was significantly higher in the NSTI group (Table 1). Only CRP and WBC cutoff values were modified for the P-LRINEC based on Youden's index. Maximal cutoff values of 20 mg/L for CRP and 20/mm^3 for WBC were applied in the logistic regression models for P-LRINEC. On univariate logistic regression, serum sodium and CRP were the only two variables significantly associated with NSTI, so these laboratory parameters were included in the multivariate model along with patient age. Based on the multivariate model, the only laboratory value significantly associated with NSTI was CRP >20 (OR 43, 95%CI 4.2–435, $p = 0.002$).

To maximize the AUC, the P-LRINEC was comprised exclusively of serum sodium <135 mEq/L and CRP >20 mg/L. Application of the original LRINEC score model provided an AUC of 0.70 whereas the AUC for the P-LRINEC score model was 0.84 ($p = 0.06$, Fig. 1). CRP in the P-LRINEC model was the most sensitive laboratory value (sensitivity: 95%) with the highest NPV (93%) whereas sodium was the most specific (specificity: 95%, Table 2).

3. Discussion

Although rare, NSTI do occur among children and, when delays in diagnosis and intervention occur, increased morbidity and mortality result [4,5]. While the LRINEC score is a validated tool commonly used to heighten suspicion for NSTI in adults, the LRINEC laboratory parameters used for adults may be deceptively normal in children, further delaying diagnosis. We evaluated these commonly collected laboratory

Table 1
The median (range) values of LRINEC laboratory values were similar between the NSTI and non-NSTI groups except for CRP which was significantly higher in the NSTI group.

Laboratory test	NSTI	Non-NSTI	*p* value
CRP (mg/L)	102 (19–485)	12.5 (2.6–190)	<0.001
WBC (per mm^3)	15.8 (2.5–33)	14.6 (4.6–43)	0.80
Hemoglobin (g/dL)	11.7 (8.0–14.6)	11.7 (6.6–14.1)	0.90
Sodium (mEq/L)	137 (126–145)	138 (134–142)	0.63
Glucose (mg/dL)	104 (47–273)	99 (67–196)	0.44
Creatinine (mg/dL)	0.4 (0.2–0.8)	0.5 (0.2–0.8)	0.32

CRP C-reactive protein, WBC white blood cells.

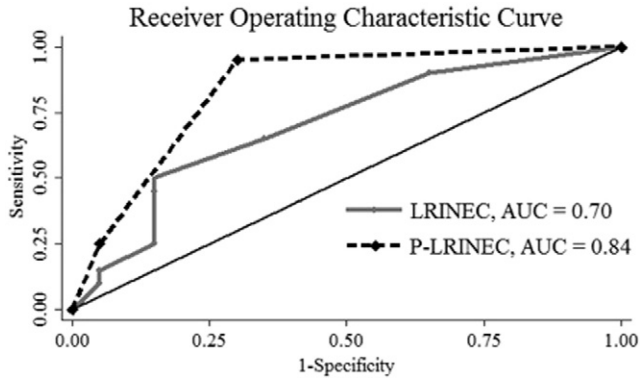

Fig. 1. The area under the receiver operating characteristic curve (AUC) was 0.84 for the P-LRINEC versus 0.70 for the LRINEC score, which implies that the P-LRINEC is a better predictive tool for pediatric NSTI than the LRINEC.

Table 2
The P-LRINEC consisted of serum CRP and sodium. A CRP >20 mg/L was the most sensitive while a sodium <135 mEq/L was the most specific.

	CRP >20 mg/L		Sodium <135 mEq/L	
	Value	95% CI	Value	95% CI
Sensitivity	95%	79–99%	25%	12–30%
Specificity	70%	54–75%	95%	82–99%
Positive predictive value	76%	63–80%	83%	39–99%
Negative predictive value	93%	72–99%	56%	48–59%
Likelihood ratio (+)	3.2	1.7–4.0	5.0	0.6–39
Likelihood ratio (−)	0.08	0.01–0.40	0.8	0.6–1.0
Accuracy	83%	66–87%	60%	47–65%

values among children and identified CRP >20 mg/L as the most sensitive and sodium <135 mEq/L as the most specific laboratory values for improving diagnostic accuracy of pediatric NSTI.

Prompt diagnosis and aggressive surgical intervention remain cornerstone principles for pediatric NSTI. However, early diagnosis in children is often difficult as the classic signs of NSTI, including fever, erythema, and bullae, may be late manifestations of this deadly disease. [1,11,12] Furthermore, in the adult population where NSTI is more common, the majority of patients with NSTI are immunocompromised or can recall a specific inciting event such as trauma [5,13]. These two factors identified in the initial history and physical should heighten a clinician's suspicion for NSTI. Unfortunately, the vast majority of children with NSTI tend to be healthy without chronic disease [5]. Our data support this as only 15% of cases had a coexisting comorbidity and 25% of cases could not recall an inciting event prior to the development of NSTI. In addition, patient age and the primary anatomic location of infection were similar between groups, and the duration of symptoms prior to presentation was only one day longer on average among non-NSTI patients. While none of our NSTI patients endorsed a recent history of varicella, this is a well-recognized risk factor for NSTI and should be elicited during patient interviews [14,15].

While clinical signs and history may not lead to early diagnosis of NSTI, imaging modalities generally lack specificity for identifying NSTI, may be time-intensive, and are not always readily available [1,16,17]. Given the nonspecific clinical history of most children with NSTI and the potential delays associated with most imaging modalities, the use of common laboratory findings may be one of the most important objective diagnostic clues leading to earlier detection and aggressive, possibly life- or limb-saving intervention. In fact, abnormal laboratory values often precede hemodynamic compromise and have been shown to help differentiate NSTI from cellulitis or abscesses [8,18].

To the best of our knowledge, this is the first study to evaluate the application of the validated LRINEC score to NSTI in a pediatric population. Wong and colleagues demonstrated that a LRINEC score ≥6 is highly predictive of NSTI with an AUC of 0.98 and a NPV 0.96 [8], yet their cohort of patients was comprised primarily of adults: 89 cases (ages 27–84) and 225 controls (ages 13–87), and there were no ages reported for their external validation cohort. Without additional data to support the utility of the LRINEC score in the pediatric population, practitioners evaluating children with severe soft tissue infections should cautiously apply the LRINEC score, if at all. A more applicable approach for pediatric NSTI would be, in addition to a thorough history and physical, to evaluate the CRP first, and if greater than 20 mg/L, to check the sodium level. Elevation of the CRP without a decrease in serum sodium should still heighten the clinician's suspicion for NSTI; with a decrease in serum sodium, the child probably warrants an urgent operative exploration.

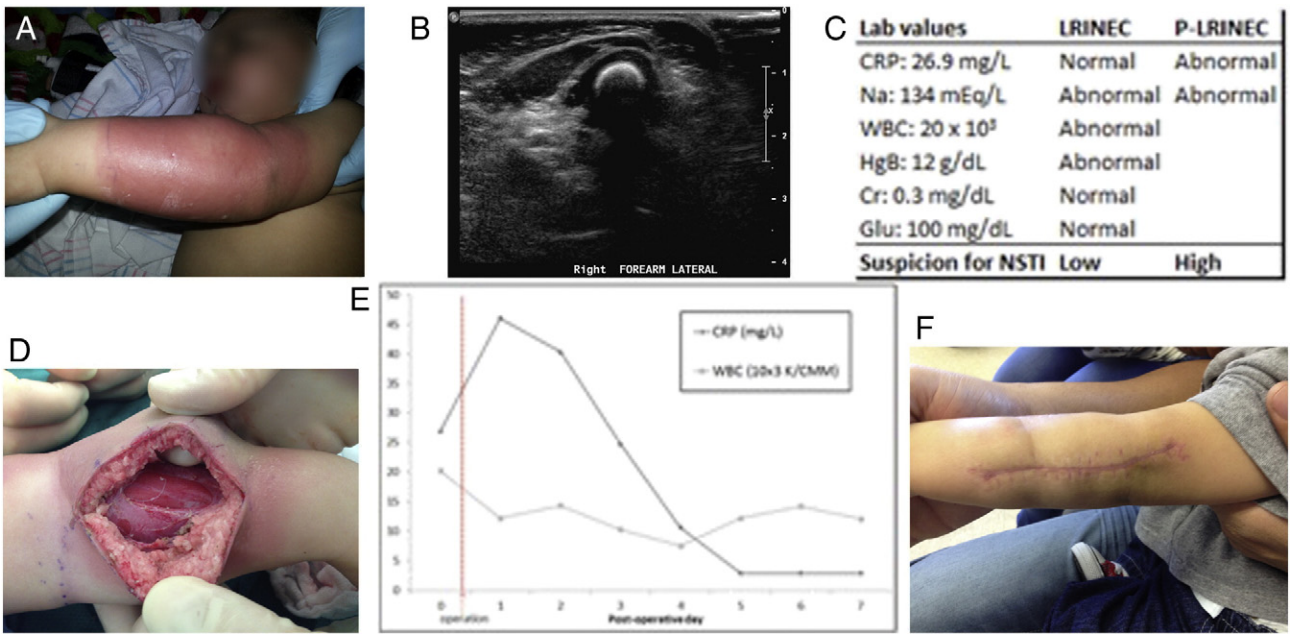

Fig. 2. The workup of possible NSTI may reveal cellulitis and nonspecific ultrasound findings as well as a low LRINEC score. Utilizing the modified values for CRP and sodium in the P-LRINEC may provide greater evidence of NSTI and prompt earlier recognition and intervention.

While no scoring system has 100% accuracy, the application of the P-LRINEC in this fashion is meant to add objective data to an often subjective diagnostic workup.

Findings concerning for NSTI in neonates should be especially alarming. Lally and colleagues reported a series of eight such patients, for whom the mortality rate was 88% [13]. The investigators suggested that the incidence of NSTI may be as high as 10% among babies with community-acquired omphalitis. Four other cases of neonatal omphalitis-related NSTI were reported by Kosloske et al. [19], and Sawin et al. reported on seven neonates with abdominal wall NSTI, five of whom died despite aggressive treatment [20]. Of note, review of the Canadian Paediatric Surveillance Program found that non-group A strep-related NSTI cases are most common in patients less one year old, especially if an infant was premature [21]. All of these studies go on to emphasize the importance of early recognition and treatment.

The value of the P-LRINEC score is demonstrated in the case of a 12 month-old boy who recently presented to our emergency department with left arm pain and cellulitis (Fig. 2a). An ultrasound revealed non-specific soft-tissue swelling (Fig. 2b). Laboratory analysis based on the LRINEC and P-LRINEC scores is shown (Fig. 2c). The patient was initiated on quadruple antibiotic therapy (vancomycin, clindamycin, penicillin G, and ciprofloxacin) and taken for emergent operative exploration, including fascial resection with skin preservation (Fig. 2d). Cultures were positive for Group A streptococcus. The patient underwent three subsequent operations and post-operative laboratory trends for CRP and WBC are shown (Fig. 2e). Decreasing CRP indicates source control. The patient was hospitalized for 13 days, did not require skin grafting, and had a complete functional recovery (Fig. 2f).

There are several limitations to this study. First, as a rare condition, our cohort is small despite the involvement of two large children's hospitals. Second, as an observational study, our results are subject to temporal confounders and regression to the mean. Furthermore, the P-LRINEC has not yet been prospectively or externally validated. Third, since the definition of NSTI is clinical and subjective, misclassification is certainly possible; however, we found that 95% of NSTI patients had tissue necrosis confirmed by pathologic specimen and most tissue cultures were positive with the expected, commonly-recognized bacteria [5,22]. Going forward, a larger multicenter, prospective study may improve the external validity of our results.

In conclusion, we found the evaluation of serum CRP and sodium to be more predictive of pediatric NSTI than the application of the original LRINEC score. Specifically, a CRP >20 mg/L alone in the setting of severe cellulitis should heighten a clinician's suspicion for NSTI. Furthermore, an accompanying decrease in serum sodium (<135 mEq/L) should be an even more concerning finding and help to encourage earlier operative intervention. While physical exam and surgeon gestalt are critical in NSTI recognition, these two laboratory values may help provide objective criteria to an otherwise subjective diagnostic workup.

References

[1] Anaya DA, Bulger EM, Kwon YS, et al. Predicting death in necrotizing soft tissue infections: A clinical score. Surg Infect 2009;10:517–22.
[2] Gunter OL, Guillamondegui OD, May AK, et al. Outcome of necrotizing skin and soft tissue infections. Surg Infect 2008;9:443–50.
[3] Kao LS, Lew DF, Arab SN, et al. Local variations in the epidemiology, microbiology, and outcome of necrotizing soft-tissue infections: A multicenter study. Am J Surg 2011;202:139–45.
[4] Majeski JA, Alexander JW. Early diagnosis, nutritional support, and immediate extensive debridement improve survival in necrotizing fasciitis. Am J Surg 1983;145:784–7.
[5] Moss RL, Musemeche CA, Kosloske AM. Necrotizing fasciitis in children: Prompt recognition and aggressive therapy improve survival. J Pediatr Surg 1996;31:1142–6.
[6] Laupland KB, Davies HD, Low DE, et al. Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. Ontario Group A Streptococcal Study Group. Pediatrics 2000;105:E60.
[7] Endorf FW, Garrison MM, Klein MB, et al. Characteristics, therapies, and outcome of children with necrotizing soft tissue infections. Pediatr Infect Dis J 2012;31:221–3.
[8] Wong CH, Khin LW, Heng KS, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004;32:1535–41.
[9] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet 2007;370:1453–7.
[10] Williams RF, Blakely ML, Fischer PE, et al. Diagnosing ruptured appendicitis preoperatively in pediatric patients. J Am Coll Surg 2009;208:819–25.
[11] Brogan TV, Nizet V, Waldhausen JH. Streptococcal skin infections. N Engl J Med 1996;334:1478.
[12] Majeski JA, John Jr JF. Necrotizing soft tissue infections: A guide to early diagnosis and initial therapy. South Med J 2003;96:900–5.
[13] Lally KP, Atkinson JB, Woolley MM, et al. Necrotizing fasciitis. A serious sequela of omphalitis in the newborn. Ann Surg 1984;199:101–3.
[14] American Academy of Pediatrics Committee on Infectious Diseases Severe invasive group A streptococcal infections: A subject reviewPediatrics 1998;101:136–40.
[15] Waldhausen JH, Holterman MJ, Sawin RS. Surgical implications of necrotizing fasciitis in children with chickenpox. J Pediatr Surg 1996;31:1138–41.
[16] Edlich RF, Cross CL, Dahlstrom JJ, et al. Modern concepts of the diagnosis and treatment of necrotizing fasciitis. J Emerg Med 2010;39:261–5.
[17] Lille ST, Sato TT, Engrav LH, et al. Necrotizing soft tissue infections: Obstacles in diagnosis. J Am Coll Surg 1996;182:7–11.
[18] Holland MJ. Application of the Laboratory Risk Indicator in Necrotising Fasciitis (LRINEC) score to patients in a tropical tertiary referral centre. Anaesth Intensive Care 2009;37:588–92.
[19] Kosloske AM, Cushing AH, Borden TA, et al. Cellulitis and necrotizing fasciitis of the abdominal wall in pediatric patients. J Pediatr Surg 1981;16:246–51.
[20] Sawin RS, Schaller RT, Tapper D, et al. Early recognition of neonatal abdominal wall necrotizing fasciitis. Am J Surg 1994;167:481–4.
[21] Eneli I, Davies HD. Epidemiology and outcome of necrotizing fasciitis in children: an active surveillance study of the Canadian Paediatric Surveillance Program. J Pediatr 2007;151:79–84.
[22] Giuliano A, Lewis Jr F, Hadley K, et al. Bacteriology of necrotizing fasciitis. Am J Surg 1977;134:52–7.