The Systemic Inflammatory Response in Patients with Appendicitis: a Progressive Phenomenon

Marcelo A. Beltrán

Received: 20 May 2014 / Accepted: 24 June 2014 / Published online: 19 July 2014
© Association of Surgeons of India 2014

Abstract The systemic inflammatory response has been described in patients with appendicitis. However, its progression from onset of symptoms to diagnosis has not been characterized. The specific purpose of this study was to describe and characterize the systemic inflammatory response to appendicitis. A descriptive cross-sectional study was conducted. One hundred eighty-three patients were studied, divided into four groups from onset of symptoms to diagnosis. The primary outcome measure was to determine the systemic inflammatory response to appendicitis according to the established groups of time intervals. The secondary outcome measure was the analysis of C-reactive protein for the same purpose. The variables of the systemic inflammatory response, according to diagnostic intervals, showed non-significant differences in white blood cell count. The temperature rose constantly after 48 h, reaching its peak after 72 h ($p=0.001$), and the respiratory rate rose after 73 h ($p<0.0001$). After 73 h, most patients had three or four systemic inflammatory response criteria ($p<0.0001$). C-reactive protein levels rose progressively, showing higher levels after 48 h ($p=0.005$). The inflammatory response to appendicitis is progressive, being more marked along the timeline from onset of symptoms to diagnosis.

Keywords SIRS · Appendicitis · C-reactive protein · Inflammatory response

M. A. Beltrán (✉)
Department of Surgery, Hospital de La Serena, P.O. Box 912,
Manuel Antonio Caro 2629, La Serena, IV Región, Chile
e-mail: beltran_01@yahoo.com

M. A. Beltrán
Emergency Unit, Hospital de La Serena, P.O. Box 912,
Manuel Antonio Caro 2629, La Serena, IV Región, Chile

M. A. Beltrán
Departamento de Clínica, Facultad de Medicina,
Universidad Católica del Norte, IV Región, Chile

Introduction

The inflammatory response to acute life-threatening conditions including appendicitis has been a subject of intensive study [1–8]. The regional and systemic responses have been described [2, 4], inflammatory parameters have been applied to diagnostic algorithms [3–6], and diagnostic scores incorporating inflammatory parameters have been developed [7, 8]. The systemic inflammatory response syndrome (SIRS) reflects the human inflammatory response to injury and infection [9]. Although the presence of SIRS has been described in patients with appendicitis, its progressive response associated with progression of clinical symptomatology has not been described and characterized. Continued systemic inflammation in patients with injury and infectious processes may result in multiple organ dysfunction and failure [1, 2, 5]. As with any acute inflammatory condition, the patients' systemic inflammatory response to appendicitis will progress, becoming more pronounced. The specific purpose of this study was to describe the systemic inflammatory response to appendicitis from the beginning of symptoms to diagnosis in patients with appendicitis submitted to emergency surgery.

Patients and Methods

Design of the Study

A prospective, descriptive cross-sectional study was conducted. At our institution, a median of 250 adult patients were submitted to emergency appendectomy every year [10]. Therefore, a sample of 152 patients with a power of 80 %, an error of 5 %, and 95 % confidence intervals was required to perform this study. During 1 year, 268 patients operated on for acute appendicitis at our institution were prospectively included; of them, 85 cases that did not comply with inclusion

criteria were excluded. A total of 183 subjects (100 %) selected according to the following criteria were studied: patients older than 15 years submitted to emergency appendectomy and appendicitis confirmed by histology. Exclusion criteria were as follows: patients with immunosuppressive or immunodepressive conditions, a pathological report describing a normal appendix, and patients submitted to appendectomy as part of another elective procedure. Patients were divided into four groups according to the interval of time calculated from the onset of symptoms, as stated by the patient, to diagnosis: group 1 from 0 to 24 h, group 2 from 25 to 48 h, group 3 from 49 to 72 h, and group 4 more than 73 h. At admission, demographic and clinical data, interval of time from onset of symptoms to diagnosis, white blood cell (WBC) count, C-reactive protein (CRP) values, and SIRS scores were recorded. The primary outcome measure was to determine the expected systemic inflammatory response to appendicitis according to the established groups of time intervals using SIRS criteria for that purpose. The secondary outcome measure was the analysis of CRP, as another inflammatory parameter which is habitually included within the diagnostic study of patients with suspected appendicitis.

Clinical Relevance of SIRS in Appendicitis

The clinical relevance of SIRS in patients with appendicitis was studied correlating SIRS scores with perforated appendicitis and postoperative complications.

Definitions and Normal Values

The interval of time measured from the onset of symptoms to diagnosis was termed “diagnostic interval.” SIRS criteria were defined as temperature higher than 38 °C or lower than 36 °C, heart rate (HR) higher than 90/min, respiratory rate (RR) higher than 20/min, and WBC higher than 12,000/mm³ or lower than 4,000/mm³; one point was assigned for every positive parameter which yielded a score from zero to four points [5, 9]. A patient was considered to have SIRS when two or more points were simultaneously present [9]. According to our

institutional laboratory, normal values were considered for WBC at <11,300/mm³ and CRP from 0 to 5 mg/L.

Statistics

Continuous variables were reported as mean±standard deviation and analyzed with the analysis of variance test. Categorical variables were reported as frequencies and analyzed with the χ^2 test. Multiple comparisons were performed with the Wilcoxon-Bonferroni test. Correlations between SIRS scores, perforated appendicitis, and postoperative complications were assessed with Pearson's test. The database was constructed with the statistical software SPSS 11.0 (Chicago, IL, USA).

Results

General Characteristics

The series was composed of 107 men (58.5 %) and 76 women (41.5 %), with a mean age of 29.7±12 years (15–77). There were 45 patients (25 %) with a diagnostic interval from 0 to 24 h, 67 patients (37 %) presented between 25 and 48 h ($p=0.002$), 38 patients (21 %) presented between 49 and 72 h, and 33 patients (18 %) presented after 73 h from the onset of symptoms. Analysis of SIRS criteria showed that 73 patients (40 %) had a temperature equal to or over 38 °C, 119 patients had a heart rate of 90/min or higher (65 %), 27 patients (15 %) had a respiratory rate of 20/min or higher, and 152 patients (83 %, $p<0.0001$) had a WBC count over 12,000/mm³. All patients (100 %) had CRP values of 5 mg/L or higher. According to the SIRS score, 11 patients (6 %) had zero point, 32 patients had one point (17 %), 83 patients (45 %, $p<0.0001$) had two points, 42 patients (23 %) had three points, and 15 patients (8 %) had four points. Consequently, 140 patients (76.5 %, $p<0.0001$) had SIRS.

SIRS Characteristics

Table 1 shows the frequency of SIRS criteria for every group of diagnostic intervals. A WBC count higher than 12,000/

Table 1 Frequency of SIRS according to diagnostic intervals

SIRS	Group 1 (0–24 h)	Group 2 (25–48 h)	Group 3 (49–72 h)	Group 4 (>73 h)
White blood cell count > 12,000/mm ³	35 (78 %)	63 (94 %)*	35 (92 %)*	19 (58 %)
Temperature >38 °C	14 (31 %)	20 (30 %)	15 (39.5 %)	24 (73 %)*
Heart rate >90/min	12 (27 %)	52 (78 %)*	29 (76 %)*	26 (79 %)*
Respiratory rate >20/min	–	–	3 (8 %)	24 (73 %)*
Total	45 (100 %)	67 (100 %)	38 (100 %)	33 (100 %)

* $p<0.0001$

mm³ was more frequent in groups 2 and 3. A temperature higher than 38 °C was more frequent in group 4. Heart rates higher than 90/min were frequently registered in group 2, remaining high in all groups thereafter. A respiratory rate higher than 20/min was frequent in group 4; other groups of diagnostic intervals did not show an increased respiratory rate, or few patients complied with this criterion. Table 2 depicts median values for SIRS variables and CRP; all median values increased progressively with progression of the diagnostic interval. CRP peaked in group 3 and increased in group 4 ($p<0.0001$). Table 3 shows the occurrence of SIRS points; patients in group 1 had fewer SIRS points compared with other groups; besides, 49 % did not have SIRS ($p<0.0001$). Most patients in group 2 had two SIRS points (66 %, $p<0.0001$); 13 patients (19 %) did not have SIRS, while 10 patients (15 %) had three SIRS points. Most patients in group 3 did have SIRS (87 %), and 21 patients (55 %) had three points ($p<0.0001$). Finally, 45 % of patients in group 4 had four SIRS points ($p<0.0001$).

The analysis of SIRS variables according to diagnostic intervals showed non-significant differences in WBC count ($p=0.475$) (Fig. 1a). The temperature rose constantly after 48 h from the onset of symptoms, reaching its peak after 73 h ($p=0.001$) (Fig. 1b). The heart rate rose constantly from the onset of symptoms, presenting higher values after 73 h ($p<0.0001$). The respiratory rate rose after 73 h from the onset of symptoms ($p<0.0001$) (Fig. 1c). CRP levels rose progressively concurrently with progression of the time interval, showing higher levels after 48 h ($p=0.005$) (Fig. 1d). After 72 h, most patients had three or four SIRS criteria ($p<0.0001$) (Fig. 1e).

Perforated Appendicitis, Postoperative Complications, and Correlations with Time Intervals and SIRS Points

The incidence of perforated appendicitis according to diagnostic intervals was 7 % for group 1, 24 % for group 2, 53 % ($p<0.0001$) for group 3, and 85 % ($p<0.0001$) for group 4; it should be noted how the incidence progresses along the timeline, increasing significantly at each established diagnostic interval. The general incidence of perforation for the cohort was 37 %. The incidence of perforation according to SIRS

points was 31 % for one SIRS point, 20 % for two SIRS points, 66 % ($p<0.0001$) for three SIRS points, and 80 % ($p<0.0001$) for four SIRS points; patients with SIRS 3 and 4 had the highest perforation rates. Correlations among perforation, time intervals, and SIRS points assessed with Pearson's test showed that the perforation rate was correlated to increased time interval and higher SIRS score ($p<0.0001$). Regarding the complication rate, there were only seven complications (4 %): six patients had a minor superficial surgical site infection that did not require surgical interventions, and one patient suffered from deep venous thrombosis (DVT); notably, the patient who suffered from DVT had a SIRS score of 3 and a diagnostic interval of more than 73 h (Table 4).

Discussion

The importance of prompt diagnosis and treatment for patients with appendicitis has been emphasized in order to avoid septic complications that increase with advanced pathology [2, 5, 11, 12]. With an increased interval between the onset of symptoms and surgery exceeding 72 h, the odds for more severe pathology were higher compared with an interval below 12 h [2, 3, 5, 6, 11, 12], and this observation was confirmed with the findings of the present study showing increased SIRS scores and diagnostic intervals related to an increased rate of perforated appendicitis. Patient delay in presenting to the emergency room after onset of symptoms was related to worsening pathology compared with in-hospital delays [11]. However, although these data support the importance of progressive inflammatory reaction to appendicitis, the proper inflammatory progression has not been characterized [12]. This is of relevance because of recent claims for conservative antibiotic management of appendicitis [13–19], the high rate of conservative treatment failure, and recurrent appendicitis indicating a problem with the design of these studies which have used unselected consecutive samples with various different diagnostic intervals, not taking into account the fact that appendicitis is an evolving disease that worsens with the passing of time.

Table 2 SIRS and CRP levels according to diagnostic intervals

Variable	Group 1 (0–24 h)	Group 2 (25–48 h)	Group 3 (49–72 h)	Group 4 (>73 h)
White blood cell count (per mm ³)	16,020±3,784 (8,300–22,700)	17,630±3,780 (11,200–24,500)	18,037±5,759* (6,200–26,700)	19,372±6,635* (10,100–27,400)
Temperature (°C)	37.7±0.4 (36.8–38.5)	37.8±0.5 (36.5–38.9)	37.8±0.9 (36–39.2)	38.4±0.6** (37.5–39.4)
Heart rate (per min)	91.3±14.1 (67–116)	106.4±14.6** (80–124)	110±22.5** (84–128)	125.8±16** (92–131)
Respiratory rate (per min)	16.4±1.4 (14–19)	16.9±1.4 (14–19)	18.3±1.3 (15–23)	22.6±2.8** (18–28)
C-reactive protein (mg/dL)	162.7±95 (39.2–400.3)	210.5±142 (63–360.5)	231±121** (90.5–410.3)	257.4±109** (95.8–450.3)

* $p=0.003$; ** $p>0.0001$

Table 3 SIRS points

SIRS	Group 1 (0–24 h)	Group 2 (25–48 h)	Group 3 (49–72 h)	Group 4 (>73 h)
0	7 (16 %)*	4 (6 %)	—	—
1	15 (33 %)*	9 (13 %)	5 (13 %)	3 (9 %)
2	23 (51 %)*	44 (66 %)*	12 (32 %)	4 (12 %)
3	—	10 (15 %)	21 (55 %)*	11 (33 %)*
4	—	—	—	15 (45 %)*
Total	45 (100 %)	67 (100 %)	38 (100 %)	33 (100 %)

* $p < 0.0001$

The inflammatory response to appendicitis is not uniformly similar in all patients; consequently, the individual particular response to injury may be considered as a source of bias. In that sense, others have reported on patients without any inflammatory response to appendicitis with frequencies as high

as 16 to 28 %; however, 52 to 80 % of those patients presented early in the diagnostic interval [2, 3]. In the present study, the frequency of patients without inflammatory response was similar to previous reports, most of them also presenting early within the diagnostic interval.

Fig. 1 **a** White blood cell count increases with progression of appendicitis. After 73 h from the onset of symptoms, median values decreased secondarily to white blood cell adhesion to capillary walls and posterior migration of leukocytes from peripheral circulation into the appendicular area. **b** Fever was mild in patients with appendicitis during the first 48 h from the onset of symptoms. After this period, the temperature rose steadily, reaching its peak after 73 h. **c** The respiratory rate remained

relatively low during the first 72 h; however, after 73 h, it significantly increased, reflecting the patients' septic compromise. **d** Progression of C-reactive protein levels was steady and consequent with progression of the diagnostic interval, being more marked after 48 h. **e** SIRS points increased with progression of the diagnostic interval; after 73 h, most patients had three or four points, and this was consequent with the instauration of the septic process

Table 4 Complications according to diagnostic intervals and SIRS scores

	Complications, <i>n</i> (%)
Diagnostic intervals	
Group 1, 0–24 h	2 (1)
Group 2, 25–48 h	3 (2)
Group 3, 49–72 h	–
Group 4, >73 h	2 (1)
SIRS score	
0	–
1	–
2	3 (2)
3	3 (2)
4	1 (0.5)

WBC

Leukocytosis is the most frequent and expected parameter to be present in patients with appendicitis and is considered the best laboratory method to support the diagnosis of uncomplicated appendicitis [4, 6, 20]. Although the absence of leukocytosis does not rule out appendicitis [3, 21], its presence supports the clinical diagnosis [2–8, 20]. It is expected that patients with advanced disease have higher WBC count due to increased polymorphonuclear cell count [5, 12, 20]. However, once the septic process is established, leukopenia may ensue. Leukocytosis was present in most patients in this study and was more frequent in patients with a diagnostic interval between 25 and 72 h. That was expected because the clinical evolution of appendicitis has its peak between 24 and 48 h after the onset [3, 5, 6, 11]. Most patients in group 1 had leukocytosis which was also expected due to the initial phase of the inflammatory process [3–6, 20]. Only 58 % of patients in group 4 had leukocytosis, and of those with leukocytosis, the value was high. Some patients had normal values, and that response was expected because the inflammatory response in this series reached its peak after 73 h and because the instauration of sepsis would eventually lead to a decreased WBC count or even leukopenia [2, 4, 5, 11, 12, 22–26]. In studies using various diagnostic intervals, the incidence of leukocytosis varied from 78 to 88 % [2, 3]; however, in one study using three different diagnostic intervals, the presence of leukocytosis increased along a prolonged time of symptom evolution [12]. A high WBC count could be expected in patients with advanced appendicitis [5, 6, 12, 20]; however, most patients presenting late within the diagnostic interval could have a lower WBC compared with patients with lesser diagnostic interval [4–6], these observations being similar to the results of the present study. Consequently, it should be expected that the WBC count would increase progressively along the diagnostic interval timeline, although after 73 h, the

median WBC count would decrease, maintaining a higher count in approximately half of the cases.

Temperature

The temperature in appendicitis is mild even in complicated cases [2]. In patients with early and advanced appendicitis, the absence of fever has been reported with a frequency between 28 and 14 %, respectively [3]. A higher fever over 38 °C has been reported in 56 % of patients with early appendicitis and 74 % patients with advanced disease [3]. Habitually, when high fever ensues, it is due to peritonitis or an abscess and represents advanced appendicitis with a long diagnostic interval [3, 20]. In this study, it was notable how the temperature increased progressively during the first 72 h from the onset of symptoms. When patients presented after 73 h, the temperature was frequently higher than 38 °C. However, the frequency of fever higher than 38 °C was around 40 % for patients presenting within 72 h from the onset of symptoms, and this finding confirms previous observations on the behavior of fever in patients with appendicitis [2, 3].

Heart Rate

An increased heart rate is expected to be correlating with the degree of fever, both responses mediated by local and systemic production of serum inflammatory mediators such as phospholipase A₂ and interleukins [2, 4]. The heart rate reached higher values rapidly after 24 h from the onset of symptoms, remaining high in all groups. After 73 h, most patients had high-frequency tachycardia, and this finding correlates with the increased temperature and the septic state of patients with longer diagnostic intervals.

Respiratory Rate

An increased respiratory rate after 72 h denotes a severe septic state and metabolic acidosis. The respiratory rate was the least common SIRS criteria met by the whole series; it had a significantly higher frequency in patients with a diagnostic interval higher than 73 h. A frequency of 34 % for this criterion has been reported in a cohort of patients with mixed diagnostic intervals [2], which was higher than the frequency found in this study, where patients with higher diagnostic intervals were less frequent cases.

SIRS

The frequency of SIRS in the present study was 76.5 % which was similar to the reported incidence ranging

from 50 to 86 % in patients with appendicitis [2, 5]. The duration of symptoms, from onset to diagnosis, is related to the severity of appendicitis [2, 5]. In this regard, it was expected that the duration of diagnostic intervals correlated with more severe inflammatory responses, and this expected outcome was demonstrated by the findings reported herein. Patients with less than 24 h of diagnostic interval had less than two SIRS points correlating with an initial inflammatory response. When the diagnostic interval was between 25 and 48 h, all patients had between one and three SIRS points, and most of them had two SIRS points; the most common criteria was increased WBC count and elevated heart rate, illustrating the initial phases of the inflammatory response with increased circulating leukocytes and tachycardia. Patients with a diagnostic interval from 49 to 72 h had one to three SIRS points; most of them had three SIRS points showing an advanced inflammatory response. Finally, patients with a diagnostic interval higher than 73 h frequently had three or four SIRS points demonstrating a full inflammatory response presenting all SIRS criteria. The WBC count increases steadily during the diagnostic interval from 0 to 72 h, and after 73 h, it decreases. This could be explained because after 73 h, most patients were in a declared septic state and WBC had undergone marginalization within the capillary wall and migrated towards the target area, and consequently, their serum numbers decreased. Other SIRS criteria will increase because, as has been described in advanced appendicitis, phospholipase A₂ and interleukins IL-1 β , IL-6, IL-8, and IL-10 increase locally and in the serum, causing high fever and consequently increased heart rate [2, 4]. While this happens, the development of metabolic acidosis increases the respiratory rate.

CRP

CRP is an unspecific inflammatory marker useful to support the clinical diagnosis of appendicitis together with WBC and clinical parameters [3, 5, 6, 8]. Higher values of CRP strongly correlate with appendicitis [3, 4, 6, 20]. With a longer diagnostic interval, CRP values would be significantly higher [3–6, 12, 20]. It has been shown that higher CRP values correlate with perforated appendicitis [5, 6, 20]. Consequently, CRP is considered a better serological marker for advanced appendicitis than WBC [4–6, 20]. In this study, the values of CRP increased constantly with the diagnostic interval, reaching higher values after 48 h, which confirms previous observations showing that CRP values were higher with advanced disease and a diagnostic interval higher than 48 h [5, 6, 20].

Conclusions

The inflammatory response to appendicitis is progressive, being more severe along the timeline from onset of symptoms until diagnosis, correlating with advanced disease presentation.

References

- Stephenson JA, Gravante G, Butler NA, Sorge R, Sayers RD, Bown MJ (2010) The systemic inflammatory response (SIRS)—number and type of positive criteria predict interventions and outcomes in acute surgical admissions. *World J Surg* 34:2757–2764
- Rivera-Chavez FA, Wheeler H, Lindberg G, Munford RS, O’Keefe GE (2003) Regional and systemic cytokine responses to acute inflammation of the vermiform appendix. *Ann Surg* 237:408–416
- Andersson RE, Hugander AP, Ghazi SH, Ravn H, Offenbartl SK, Nyström PO et al (1999) Diagnostic value of disease history, clinical presentation, and inflammatory parameters of appendicitis. *World J Surg* 23:133–148
- Grönroos JM, Forsström JJ, Irjala K, Nevalainen TJ (1994) Phospholipase A₂, C-reactive protein and white blood cell count in the diagnosis of acute appendicitis. *Clin Chem* 40:1757–1760
- Beltrán MA, Méndez PE, Barrera RE, Contreras MA, Wilson CS, Cortes VJ et al (2009) Is hyperbilirubinemia in appendicitis a better predictor of perforation than C-reactive protein? A prospective study. *Indian J Surg* 71:265–272
- Ortega-Deballon P, Ruiz de Adana-Belbel JC, Hernández-Matías A, García-Septiem J, Moreno-Azcoita M (2008) Usefulness of laboratory data in the management of right iliac fossa pain in adults. *Dis Colon Rectum* 51:1093–1099
- Andersson M, Andersson RE (2008) The appendicitis inflammatory response score: a tool for the diagnosis of acute appendicitis that outperforms the Alvarado score. *World J Surg* 32:1843–1849
- De Castro SM, Ünlü Ç, Steller EP, van Wagenveld BA, Vrouenraets BC (2012) Evaluation of the appendicitis inflammatory response score for patients with acute appendicitis. *World J Surg* 36:1540–1545
- Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, International Sepsis Definitions Conference et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Intensive Care Med* 29:530–538
- Beltrán MA (2012) Right hemicolectomy in patients operated on for acute appendicitis: from the McBurney incision and appendectomy to the midline laparotomy and hemicolectomy. *Rev Colomb Cir* 27: 129–138
- Ditillo MF, Dziura JD, Rabinovici R (2006) Is it safe to delay appendectomy in adults with acute appendicitis? *Ann Surg* 244: 656–660
- Wu HP, Huang CY, Chang YJ, Chou CC, Lin CY (2006) Use of changes over time in serum inflammatory parameters in patients with equivocal appendicitis. *Surgery* 139:789–796
- Hansson J, Kömer U, Ludwigs K, Johnsson E, Jönsson C, Lundholm K (2012) Antibiotics as first-line therapy for acute appendicitis: evidence for a change in clinical practice. *World J Surg* 36:2028–2036
- Fitzmaurice GJ, McWilliams B, Hurreiz H, Epanomeritakis E (2011) Antibiotics versus appendectomy in the management of acute appendicitis: a review of the current evidence. *Can J Surg* 54:307–314
- Mason RJ (2008) Surgery for appendicitis: is it necessary? *Surg Infect* 9:481–488

16. Andersson RE, Petzold MG (2007) Nonsurgical treatment of appendiceal abscess or phlegmon: a systematic review and meta-analysis. *Ann Surg* 246:741–748
17. Styrud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G et al (2006) Appendectomy versus antibiotic treatment in acute appendicitis. A prospective multicenter randomized controlled trial. *World J Surg* 30:1033–1037
18. Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K (2009) Randomized clinical trial of antibiotic therapy versus appendectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg* 96:473–481
19. Malik AA, Bari U (2009) Conservative management of acute appendicitis. *J Gastrointest Surg* 13:966–970
20. Andersson RE, Hugander A, Ravn H, Offenbartl K, Ghazi SH, Nyström PO et al (2000) Repeated clinical and laboratory examinations in patients with an equivocal diagnosis of appendicitis. *World J Surg* 24:479–485
21. Monneuse O, Abdalla S, Pilleul F, Hervieu V, Gruner L, Tissot E et al (2010) Pain as the only consistent sign of acute appendicitis: lack of inflammatory signs does not exclude the diagnosis. *World J Surg* 34: 210–215
22. Guidet B, Aegerter P, Gauzit R, Meshaka P, Dreyfuss D (2005) Incidence and impact of organ dysfunctions associated with sepsis. *Chest* 127:942–951
23. Schein M, Marshall J (2004) Source control for surgical infections. *World J Surg* 28:638–645
24. De Waele JJ (2010) Early source control in sepsis. *Langenbecks Arch Surg* 395:489–494
25. Hynninen M, Wennervirta A, Leppäniemi A, Pettilä V (2008) Organ dysfunction and long term outcome in secondary peritonitis. *Langenbecks Arch Surg* 393:81–86
26. Zhao H, Heard SO, Mullen MT, Crawford S, Goldberg RJ, Frenkl G et al (2012) An evaluation of the diagnostic accuracy of the 1991 American College of Chest Physicians/Society of Critical Care Medicine and the 2001 Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society sepsis definition. *Crit Care Med* 40:1700–1706