settings (9). Thus, some of the variability presented here may be due to inherent technical variation in the analyses, and we are intrigued to see what a prospective validation study with clinically optimized technologies will provide.

Severe infections leading to sepsis create a complex pro- and anti-inflammatory response with associated life-threatening organ dysfunction. Dysregulation of the inflammatory and host protective immune responses can lead to multiple organ failure and death, as well as to chronic critical illness and life-long morbidity. Discovery-based studies have demonstrated different patterns of gene expression associated with viral and bacterial infections, trauma, and burns, as well as for differential clinical outcomes, and potentially response to therapeutic interventions (5, 9, 10). The current study by Sweeney and Khatri (4) in this issue of *Critical Care Medicine* provides a road map for the discovery and validation of unique genomic biomarkers for a variety of clinical questions in the critically ill patient. It also births the question of whether we can use new bioinformatics and computational models to identify new genes that may contribute to a specific disease process. Enthusiasm for these genomic biomarkers must be tempered by the failure of numerous earlier protein biomarkers in sepsis (11). History tells us to remain skeptical that a single biomarker will be sufficient to prove clinically useful in such a complex phenotype as sepsis. Future diagnostic tests during sepsis may require a combination of existing and/or future biomarkers. However, Sweeney and Khatri (4) make a significant step forward and remind us that the massive amounts of public data collected since the inception of National Institutes of Health Gene Expression Omnibus in 2002 are an untapped source of knowledge (12). Future efforts will make the transition from discovery and validation to the clinical application of these and other tools more timely and cost-effective.

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Source Control in Sepsis Urgent or Not So Fast?*

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In this issue of *Critical Care Medicine*, Martínez et al (1) present some remarkable findings with significant clinical ramifications when caring for patients requiring source control for sepsis management. The investigative team did a detailed analysis from a large, multi-institutional collaborative database from 99 ICUs in Spain. They evaluated pooled data from 3,663 patients with new onset, infection-related, organ dysfunction (now referred to as "sepsis or septic shock" [2, 3]) in a prospective, observational clinical study. The authors focused upon the impact of source control interventions in determining the ICU and hospital mortality rate in the management of sepsis. They also investigated the relationship between and the timing between recognition of the need for source control and the actual initiation of source control measures, be they percutaneous drainage or surgical procedures.

The investigators find that patients requiring source control ($n = 1{,}173$ [32%]) were significantly older (66.7 vs 62.8 yr; $p < 0.001$) and more likely to be in shock (73.9 vs 65.5; $p < 0.001$) with bacteremia, elevated lactate levels, and other standard measures of disease severity and multiple organ dysfunction than the 2,490 contemporary septic patients not

*See also p. 11.

Key Words: sepsis; sepsis management; septic shock; source control

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requiring source control (1). Despite features that would predict a worse outcome for patients requiring source control, these patients fared better overall with a crude ICU mortality rate of only 21.2% versus the no source control, comparator population (25.1%; $p = 0.01$), even after adjusting for potential confounders. Importantly, the survival advantage in the source control group persisted even though overall compliance with the sepsis resuscitation bundles was significantly inferior to the nonsource control patients. However, the source control group ultimately ended up with a higher percentage of patients receiving appropriate antimicrobial use than the no need for source control group (57.1 vs 49.4%; $p < 0.001$).

In contrast to the conventional wisdom and a number of other observational studies (4–10), no differences in outcome could be detected that were attributable to the timing of the source control procedures whether source control was performed percutaneously by interventional radiologists or by surgeons in the operating room (1). A very similar, multicenter, observational study, conducted in Germany during the same time period as the current study, reported significantly worse outcomes in patients whose source control interventions were performed more than 6 hours after onset when compared with earlier intervention times (7). Other studies have found that a 12-hour cutoff is a better indicator between early and late intervention times with better outcomes observed in the early intervention groups (9, 10).

How do we reconcile these observational findings and differences in determining the need and the optimal timing for source control in septic patients? These observations need to be viewed in a clinical context with contemporary critical care practice. We must acknowledge that large observational studies from this Spanish cooperative multicenter database, and similar collaborative critical care study groups, provide extremely valuable, clinically relevant, information when addressing questions such as the value of source control in sepsis. Despite their considerable value and intrinsic utility, retrospective observational studies, looking back at outcomes from nonrandomized subgroups, are susceptible to systematic error from unintended bias (11).

The major statistical issue is allocation bias where one assumes that the study group (e.g., early intervention source control subgroup) and the comparator subgroup (e.g., late intervention group) are drawn from the same subpopulation (patients needing source control to manage their septic event). This assumption in retrospective studies, no matter how well intended, is often subject to selection bias (11). First, source control versus nonsource control septic patients are clearly different patient populations when considering the source of infection leading to sepsis. Source control patients usually have intra-abdominal infections, necrotizing soft tissue infections, obstructive nephropathy, or some form of infected foreign body or catheter that needs to be removed. Conversely, nonsource control septic patients usually have pneumonia, CNS infections, or nonnecrotizing soft tissue or bone/joint infections. The differences in outcome observed in this study could very well be the intervention under study itself, as logically surmised by the investigators. However, distinct differences exist in the nature of the infecting pathogens at these anatomic sites and local tissue conditions, repair capacity, and functional tolerance to infection from nondrainable infected sites in the noninterventional and interventional patient subgroups. Perhaps the differences in outcomes are related to the distinguishable characteristics of the pathogens or the host tissue repair capacity rather than the source control procedure itself. Furthermore, draining an infected tissue space during source control maneuvers provides excellent specimens to determine, with considerable diagnostic accuracy, the precise nature of the offending microbial pathogen. This provides unambiguous determination of the pathogen thereby allowing for targeted antimicrobial therapy to a much greater extent in the patients undergoing source control than the nonsource control group. It is worth noting that the final antimicrobial choice was significantly more likely to be deemed effective in the source control group rather than the noninterventional subgroup (1).

The second major finding in this study report is the apparent absence of evidence of outcome differences based upon the timing of intervention in the source control group of patients. Here again there might be a nondetectable and unmeasured bias in who gets selected for early intervention versus later intervention. Two competing clinical imperatives come into play when assessing a desperately ill patient in septic shock before deciding to proceed to the operating room for source control: 1) drain the abscess, reduce the bacterial load (12), and remove necrotic tissue as soon as possible before the patient deteriorates into irreversible shock; or 2) stabilize the patient's hemodynamics and physiologic status as the first priority and then do the surgery in as an elective procedure when the patient is stable and tissue planes are better defined (13).

The natural inclination is to take the second option by stabilizing the patient first and then proceeding to source control later under more controlled circumstances. There are times when clinicians are forced to move to invention immediately in some situations such as a large intra-abdominal abscess ready to spontaneously rupture, rapidly spreading necrotizing fasciitis, or clostridial myonecrosis. This decision have become less risky by the availability and capability to do minimally invasive, percutaneous drainage procedures early, thereby removing the necessity or at least delaying the need for definitive surgery until the patient is stabilized. Every patient presents with their own unique set of differing circumstances, comorbidities, immune functional status, etc., that might favor one approach over another. These critical differences are difficult if not impossible to define and fully account for in retrospective studies. It is perhaps not surprising that these investigators were unable to find a clear threshold level of duration of time before delayed source control institution was found to be detrimental. A gradation of the risk-to-benefit ratio from early to late invention likely exists in such patient populations. In the animal laboratory, it is possible to demonstrate a threshold concentration of bacterial mass or load that is uniformly lethal despite therapeutic attempts to salvage these animals (12, 14). A similar situation likely exists in humans, but the

pathogenicity of the infecting organism, immune capabilities of the host, and physiologic reserves in each septic patient are highly variable and will ultimately determine outcome.

This study finding does not excuse care givers to default to a lackadaisical approach in this critically ill, vulnerable patient population. Rather this study supports the notion that personalized medicine and surgery is the optimal approach for the timing of source control in septic patients. Some patients need early intervention, whereas others can probably have source control delayed safely until their clinical status has improved. It is difficult to conceive of a situation where a prospective, randomized, clinical trial could be designed to rigorously determine to optimal time for initiation of source control in septic patients. Such a study might be possible but would be hard to justify on ethical grounds. The present evidence indicates that a careful look for a drainable focus of infection is mandatory in all septic patients. The timing of source control interventions, should the need arise, is a challenging, difficult, individual decision, which needs to be made based upon the totality of evidence for each patient.

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Is It HIT?*

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No doubt, heparin-associated thrombocytopenia (HIT) can be a devastating syndrome with severe, life-threatening arterial and/or venous thromboembolism. HIT is a well-known phenomenon that can occur in the second week after onset of heparin therapy. It is caused by antibodies against neoepitopes in a complex formed by heparin and platelet factor 4 (PF4), a protein that is released from platelets upon activation (1). Interestingly, PF4 can also bind to some bacterial structures, DNA and RNA fragments, leading to antibody formation (2). When these anti–heparin-PF4 antibodies bind their target, crosslinking of Fc receptors on platelets and monocytes occurs, causing activation and release of microparticles and tissue factor, thrombocytopenia, thrombin generation, and fibrin formation (1). This already well-known pathophysiology can explain the large variability of HIT among patient populations and the risk factors for the development of HIT. The type of heparin, duration of heparin therapy, clinical setting, surgery, infections, age, and gender are well-known risk factors for the development of HIT (1, 3).

The frequency of HIT with unfractionated heparin (UFH) or after cardiac surgery is estimated to be about 1%, with low-molecular-weight heparins (LMWH) about 0.1% (2). However, there is a major discussion about the reliability of these numbers, the clinical importance of HIT, and optimal diagnostic and therapeutic strategies. A scoring system, based on clinical variables, is used since many years and has been proven to be

***See also p. 28.**

Key Words: critical illness; heparin/adverse effects; heparin-induced thrombocytopenia; thrombocytopenia/diagnosis; thrombocytopenia/drug therapy; thromboembolism

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Impact of Source Control in Patients With Severe Sepsis and Septic Shock*

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Objectives: Time to clearance of pathogens is probably critical to outcome in septic shock. Current guidelines recommend intervention for source control within 12 hours after diagnosis. We aimed to determine the epidemiology of source control in the management of sepsis and to analyze the impact of timing to source control on mortality.

Design: Prospective observational analysis of the Antibiotic Intervention in Severe Sepsis study, a Spanish national multicenter educational intervention to improve antibiotherapy in sepsis.

Setting: Ninety-nine medical-surgical ICUs in Spain.

Patients: We enrolled 3,663 patients with severe sepsis or septic shock during three 4-month periods between 2011 and 2013.

Interventions: Source control and hospital mortality.

Measurements and Main Results: A total of 1,173 patients (32%) underwent source control, predominantly for abdominal, urinary, and soft-tissue infections. Compared with patients who did not require source control, patients who underwent source control were older, with a greater prevalence of shock, major organ dysfunction, bacteremia, inflammatory markers, and lactic acidemia. In addition, compliance with the resuscitation bundle was worse in those undergoing source control. In patients who underwent source control, crude ICU mortality was lower (21.2% vs 25.1%; $p = 0.010$); after adjustment for confounding factors, hospital mortality was also lower (odds ratio, 0.809 [95% CI, 0.658–0.994]; $p = 0.044$). In this observational database analysis, source control after 12 hours was not associated with higher mortality (27.6% vs 26.8%; $p = 0.789$).

Conclusions: Despite greater severity and worse compliance with resuscitation bundles, mortality was lower in septic patients who underwent source control than in those who did not. The time to source control could not be linked to survival in this observational database. (*Crit Care Med* 2017; 45:11–19)

Key Words: critical care; infection control; mortality; sepsis; septic shock; severe sepsis

***See also p. 130.**

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Sepsis is an inflammatory response to severe infection with organ dysfunction (1). Infection initiates cytokine release, leading to a global inflammatory cascade. Under the recent hypothesis that bacterial load is the primary driver of septic organ dysfunction, the rapid clearance of pathogens is the central determinant of outcome in septic shock (2), and early appropriate antimicrobial therapy and source control are key to sepsis management.

Source control comprises "all physical measures to eliminate sources of infection, to control contamination, and to restore anatomy and function" (3). It includes draining infected fluids, debriding infected soft tissues, removing infected devices or foreign bodies, and correcting anatomic derangement causing microbial contamination. Source control's effectiveness depends on the infection site, the patient's premorbid state, and the resources available (4).

The Surviving Sepsis Campaign (SSC) recommends all patients with severe sepsis or septic shock be evaluated as soon as possible for specific infection sites amenable to source control and undergo source control within 12 hours after diagnosis (grade 1C, SSC 2012) (5). However, source control has received less attention than other treatments in the SSC. In addition, although studies show that early compliance with the SSC bundles is associated with lower mortality (6–8), evidence regarding the impact of the timing of source control in patients with severe sepsis or septic shock is lacking.

The impact of source control in septic patients is not fully understood. We aimed to assess the epidemiology of the need for source control and its role in the management of patients with severe sepsis or septic shock. We hypothesized that delays in source control after onset of severe sepsis or septic shock would worsen outcome.

MATERIALS AND METHODS

Study Design

We conducted a prospective secondary analysis of the Antibiotic Intervention in Severe Sepsis study, a Spanish national multicenter educational intervention in 99 medical-surgical ICUs homogeneously distributed throughout Spain. All consecutive adults with severe sepsis or septic shock admitted to participating ICUs during three 4-month periods (April to July 2011, April to July 2012, and January to April 2013) were eligible for the study.

Each center's ethics committee approved the study and waived the informed consent requirement due to the study's observational and anonymous nature.

The study design, data collection, and quality control measures are in detailed in Appendix S1 (Supplemental Digital Content 1, http://links.lww.com/CCM/C27). Severe sepsis was defined as sepsis associated with organ dysfunction unexplained by other causes. Septic shock was defined as sepsis associated with systolic blood pressure less than 90 mm Hg, mean arterial pressure less than 65 mm Hg, or a reduction in systolic blood pressure more than 40 mm Hg from baseline despite adequate volume resuscitation (9).

Process of Care and Outcome Measurements

We recorded demographic characteristics (age and sex), Charlson comorbidity score, presence of shock, diagnosis at admission (medical, emergency surgery, and elective surgery), site of infection, type of infection (community acquired, healthcare related, hospital acquired, or ICU acquired), organ dysfunction at sepsis presentation, worst value of inflammatory markers (C-reactive protein and procalcitonin) in the first 24 hours of sepsis onset, presence of bacteremia, need for source control, and worst Acute Physiology and Chronic Health Evaluation II score during the first 24 hours in the ICU.

Attending physicians decided when specific percutaneous or surgical source control were necessary. **Appendix S2** (Supplemental Digital Content 2, http://links.lww.com/CCM/C28) describes the source control techniques in detail. We recorded time from onset of severe sepsis or septic shock to source control and divided patients into those who received early (< 12 hr) and late (≥ 12 hr) source control. We also recorded time from onset to other acts and targets prescribed in the SSC guidelines (10): measuring serum lactate, obtaining blood cultures, administering broad-spectrum antibiotics, administering fluids and/or vasopressors in patients with hypotension and/or lactate more than 4 mmol/L (36 mg/dL), and achieving central venous pressure greater than or equal to 8 mm Hg and central venous oxygen saturation greater than or equal to 70%. We also recorded the appropriateness of antibiotic therapy, defined as the administration of an antimicrobial agent with in vitro microbiologic activity against the isolated pathogen. To facilitate antibiotic prescription, researchers used preferentially their local guideline or an electronic clinical decision support system (http://www.es.dgai-abx.de).

Patients were followed up until death or hospital discharge. The primary outcome variable was hospital mortality. Secondary outcome measures included days of mechanical ventilation, days of vasopressors, hospital and ICU lengths of stay, and ICU mortality.

Statistical Analysis

Descriptive statistics included frequencies and percentages for categorical variables and means, SD, CIs, medians, and interquartile ranges for continuous variables. To compare continuous variables, we used Student *t* test or the Mann-Whitney *U* test as appropriate. To analyze categorical variables, we used the chi-square test or Fisher exact test as appropriate.

To assess the impact of source control, we used multivariate logistic regression with ICU and hospital mortality as the dependent variables and source control, age, sex, Acute Physiology and Chronic Health Evaluation II score, the presence of shock, Charlson comorbidity score, patient location at sepsis diagnosis, site of infection, appropriateness of antibiotic therapy, and compliance with early antibiotic administration and resuscitation with fluids and/or vasopressors as independent variables.

In the group who underwent source control, we did a multivariable analysis to assess the impact of time to source control (< 12 vs ≥ 12 hr) on hospital mortality, including the same variables as in the previous model. To better understand the importance of time to source control, we applied the same regression model for abdominal, urologic, and skin and soft-tissue infections.

We also examined time to source control as a continuous variable. To determine the best cutoff time to source control to discriminate mortality, we plotted a receiver operating characteristic curve (ROC) and calculated the area under the curve (AUC).

Statistical tests were two tailed with significance defined as p value less than 0.05. We used SPSS version 15.0 (SPSS, Chicago, IL) for all analyses.

RESULTS

Patients Undergoing Source Control Versus Those Who Did Not

A total of 3,663 patients met the criteria for severe sepsis or septic shock during the study periods; 1,173 (32%) of these underwent surgical or percutaneous procedures for source control. **Table 1** summarizes patients' demographics, preexisting medical conditions, and baseline clinical, physiologic, and laboratory variables. Compared with patients who did not require source control, patients undergoing source control were older, and a higher proportion had shock. Coagulopathy, hyperlactatemia, and heart, kidney, and liver failures were more common in patients who required source control. Patients who required source control had more bacteremic episodes and higher levels of C-reactive protein and procalcitonin. The most common source of sepsis was abdominal infection in patients undergoing source control (n = 788; 67.2%) and respiratory infection in patients who did not require source control (n = 1,189; 47.8%). A greater proportion of patients in the source control group were admitted after urgent surgery and had hospital-acquired infections.

Compliance with three of the six tasks in the 6-hour resuscitation bundle (lactate measurement, blood cultures before antibiotics, and early administration of broad spectrum antibiotics) was worse in patients requiring source control than in those who did not. Overall compliance with all elements in the resuscitation bundle was also lower in patients requiring source control (**Table 2**).

Table 3 reports the outcome data for patients who required source control versus those who did not. Patients who required source control needed more days of vasopressor treatment, but no differences were observed in days of mechanical ventilation. The hospital stay was longer in patients who required source control (32.5 vs 27.4 d in those that did not; $p < 0.001$); the ICU stay was similar in the two groups. ICU mortality was lower in patients requiring source control (21.2% vs 25.1%; $p = 0.010$), but hospital mortality was similar in the two groups. After adjusting for possible confounders, ICU mortality remained lower in patients who underwent source control (**Table S1**, Supplemental Digital Content 3, http://links.lww.com/CCM/C29), and hospital mortality was also lower in patients undergoing source control (odds ratio, 0.809 [95% CI, 0.658–0.994]; $p = 0.044$) (**Table 4**).

Timing of Source Control

A total of 1,173 patients (32%) underwent procedures for source control, and time was recorded in 1,090 of these; thus, 83 patients were excluded because time to source control was unknown. Median time to source control was 4.6 hours (1–11.5 hr). Interventions for source control were done within 12 hours of sepsis onset in 825 patients (75.7%). No significant differences in demographic or clinical characteristics were found between patients who underwent source control within 12 hours of onset and those who underwent source control later (**Table S2**, Supplemental Digital Content 4, http://links.lww.com/CCM/C30). Compliance with the items in the 6-hour resuscitation bundle was better in patients undergoing source control within 12 hours of onset than in those undergoing source control later, except blood cultures before antibiotics and early administration of broad-spectrum antibiotics, where no differences were observed (**Table S3**, Supplemental Digital Content 5, http://links.lww.com/CCM/C31).

Table 5 reports the outcome data for patients who underwent source control within 12 hours of onset versus those who underwent source control later. No significant differences between the two groups were observed in hospital stay, ICU stay, hospital mortality, or ICU mortality.

ROC curves analyzing time to source control as a continuous variable failed to identify a point of maximum sensitivity and specificity to predict the optimum time for source control; we observed no relationship between time to source control and mortality in the group of patients who underwent source control (AUC = 0.504, nonsignificant [ns]) (**Fig. S1**, Supplemental Digital Content 6, http://links.lww.com/CCM/C32; legend, Supplemental Digital Content 17, http://links.lww.com/CCM/C43) or in the subgroups of patients who underwent percutaneous source control (AUC = 537, ns) (**Fig. S2**, Supplemental Digital Content 7, http://links.lww.com/CCM/C33; legend, Supplemental Digital Content 17, http://links.lww.com/CCM/C43) or surgical source control (AUC = 523, ns) (**Fig. S3**, Supplemental Digital Content 8, http://links.lww.com/CCM/C34; legend, Supplemental Digital Content 17, http://links.lww.com/CCM/C43).

When we analyzed the outcomes for patients who needed source control in the subgroups with abdominal, urinary, and skin and soft-tissue infections, we found no significant differences between the less than 12 hour and greater than or equal to 12 hour groups, except longer duration of vasopressors in patients with skin and soft-tissue infections (early source control: 4.3 d vs late source control: 8.6 d; $p < 0.001$) (**Table S4**, Supplemental Digital Content 9, http://links.lww.com/CCM/C35; **Table S5**, Supplemental Digital Content 10, http://links.lww.com/CCM/C36; and **Table S6**, Supplemental Digital Content 11, http://links.lww.com/CCM/C37).

Univariate analysis found no difference in time to source control between survivors and nonsurvivors (**Table S7**, Supplemental Digital Content 12, http://links.lww.com/CCM/C38). Multivariable logistic regression adjusting for possible confounders showed no relationship between time to source control less than 12 hours and hospital mortality in the group of patients who underwent source control (**Table S8**, Supplemental Digital Content 13, http://links.lww.com/CCM/C39) or in the subgroups of patients with abdominal, urinary, and skin and soft-tissue infections (**Table S9**, Supplemental Digital Content 14, http://links.lww.com/CCM/C40; **Table S10**, Supplemental Digital Content 15, http://links.lww.com/CCM/C41; and **Table 11**, Supplemental Digital Content 16, http://links.lww.com/CCM/C42).

TABLE 1. Demographic and Clinical Characteristics of Patients

Patient Characteristic	All Patients, *n* = 3,663	Patients Not Requiring Source Control, *n* = 2,490 (68%)	Patients Requiring Source Control, *n* = 1,173 (32%)	*p*
General data				
Age (yr), mean (SD)	64 (15.1)	62.8 (15.2)	66.7 (14.6)	< 0.001
Sex (male), *n* (%)	2,319 (63.3)	1,621 (65.1)	698 (59.5)	0.001
Acute Physiology and Chronic Health Evaluation II, mean (SD)	21.8 (8.01)	22.03 (8.2)	21.3 (7.6)	0.010
Shock, *n* (%)	2,497 (68.2)	1,630 (65.5)	867 (73.9)	< 0.001
Charlson comorbidity score, mean (SD)	2.6 (2.3)	2.6 (2.3)	2.7 (2.2)	0.531
C-reactive protein (mg/dL), mean (SD)[a]	24.2 (13.7)	23.6 (13.9)	25.5 (12.9)	< 0.001
Procalcitonin (ng/mL), mean (SD)[b]	26.2 (37.6)	24.1 (34.7)	31.2 (43)	0.001
Bacteremia, *n* (%)	1,211 (40.1)	821 (37.9)	390 (45.5)	< 0.001
Appropriate antibiotic therapy, *n* (%)	1,911 (51.9)	1,231 (49.4)	670 (57.1)	< 0.001
Organ failure at sepsis presentation, *n* (%)				
No. of organ failures (SD)	2.98 (1.4)	2.98 (1.4)	2.98 (1.4)	0.914
Cardiovascular	3,019 (82.4)	1,994 (80.1)	1,025 (87.4)	< 0.001
Respiratory	1,602 (43.7)	1,275 (51.2)	327 (27.9)	< 0.001
Renal	2,068 (56.5)	1,351 (54.3)	717 (61.1)	< 0.001
Hyperbilirubinemia	606 (16.5)	386 (15.5)	220 (18.8)	0.013
Thrombocytopenia	856 (23.4)	620 (24.9)	236 (20.1)	0.001
Coagulation	1,143 (31.2)	749 (30.1)	394 (33.6)	0.032
Hyperlactatemia	1,630 (44.5)	1,056 (42.4)	574 (48.9)	< 0.001
Site of infection, *n* (%)				
Abdominal	1,234 (33.7)	446 (17.9)	788 (67.2)	< 0.001
Respiratory	1,232 (33.6)	1,189 (47.8)	43 (3.7)	
Urologic	606 (16.5)	459 (18.4)	147 (12.5)	
Skin and/or soft tissue	258 (7.0)	140 (5.6)	118 (10.1)	
Central nervous system	87 (2.4)	82 (3.3)	5 (0.4)	
Other	246 (6.7)	174 (7.0)	72 (6.1)	
Type of infection (acquisition site), *n* (%)				
Community acquired	2,285 (62.4)	1,607 (64.5)	678 (57.8)	< 0.001
Healthcare related	438 (12)	318 (12.8)	120 (10.2)	
Hospital acquired	780 (21.3)	443 (17.8)	337 (28.7)	
ICU acquired	160 (4.4)	122 (4.9)	38 (3.2)	
Diagnosis at admission, *n* (%)				
Medical	2,567 (70.1)	2,256 (90.6)	311 (26.5)	< 0.001
Surgical	205 (5.6)	109 (4.4)	96 (8.2)	
Urgent surgical	891 (24.3)	125 (5)	766 (65.3)	

[a]*n* = 2,763 patients.
[b]*n* = 2,084 patients.

TABLE 2. Compliance With Sepsis Resuscitation Bundle in Source Control Group Versus Nonsource Control Group

Sepsis Resuscitation Bundle, 6 h, *n* (%)	All Patients, *n* = 3,663	Patients Not Requiring Source Control, *n* = 2,490	Patients Requiring Source Control, *n* = 1,173	*p*
All resuscitation measures	379 (10.3)	279 (11.2)	100 (8.5)	0.013
Measure lactate	2,709 (74.0)	1,876 (75.3)	833 (71.0)	0.005
Blood cultures before antibiotics	1,906 (52.0)	1,376 (55.3)	530 (45.2)	< 0.001
Early broad-spectrum antibiotics	2,550 (69.6)	1,763 (70.8)	787 (67.1)	0.023
Fluids and vasopressors	2,152 (58.7)	1,452 (58.3)	700 (59.7)	0.434
Central venous pressure, ≥ 8 mm Hg	1,609 (43.9)	1,113 (44.7)	496 (42.3)	0.170
Central venous oxygen saturation, ≥ 70%	1,236 (33.7)	849 (34.1)	387 (33.0)	0.510

TABLE 3. Outcome Measurements in Source Control Group Versus Nonsource Control Group

Outcome Measurements	All Patients, *n* = 3,663	Patients Not Requiring Source Control, *n* = 2,490	Patients Requiring Source Control, *n* = 1,173	*p*
Duration of mechanical ventilation, d, mean (SD)	6.88 (13.2)	6.78 (13.0)	7.11 (13.6)	0.480
Duration of vasopressors, d, mean (SD)	4.26 (7.2)	4.01 (6.6)	4.8 (8.4)	0.002
ICU stay, d, mean (SD)	11.8 (15.4)	11.6 (15.03)	12.3 (16.02)	0.202
Hospital stay, d, mean (SD)	29.04 (28.6)	27.4 (27.8)	32.5 (30.1)	< 0.001
Mortality, *n* (%)				
ICU	875 (23.9)	626 (25.1)	249 (21.2)	0.010
Hospital	1,088 (29.7)	756 (30.4)	332 (28.3)	0.203

DISCUSSION

This prospective observational study in patients with severe sepsis and septic shock found significantly lower mortality, even after adjustment for confounding factors, in patients who underwent measures for source control than in those who did not, despite the greater risk of death in patients who underwent source control. These findings underline the importance of source control in the management of patients with severe sepsis or septic shock.

In this large population of patients with severe sepsis or septic shock, one third of all patients underwent source control. Another recent prospective observational multicenter study including 1,011 patients with severe sepsis or septic shock reported that 41.7% underwent source control (11). The characteristics of the patients and most importantly the site of infection in this study were similar to those in our study (12).

Compared with patients who did not require source control, a higher proportion of patients who underwent source control presented shock and major organ dysfunction, probably because of higher bacterial load as suggested by the higher rates of bacteremia and higher levels of procalcitonin and C-reactive protein biomarkers that correlate with the inflammatory response. Serum procalcitonin increases with the severity of sepsis and organ dysfunction (13–16). A greater proportion of patients in the group who underwent source control had undergone surgery, and manipulation of a focus with a high microbial load might explain the higher rates of bacteremia and more severe inflammatory response (3). In addition, patients who underwent source control were older and a greater proportion had abdominal and nosocomial infections, factors independently associated with mortality (12, 17). Although patients who required source control received more appropriate antibiotherapy, the time to first antibiotic administration was longer in this group, and delays in antibiotic administration over the first 6 hours after sepsis identification are associated with increased mortality (7). Furthermore, compliance with two other tasks in the resuscitation bundle (blood cultures before antibiotic administration and lactate measurement) was worse in patients who required source control. It is unclear why there should be differences in compliance based on the use of source control, but delays might be because of prioritizing source control when needed.

Thus, although patients who underwent source control were at a greater risk than those who did not, they had lower mortality even after adjustment for confounding factors. These findings strongly support the importance of source control and lend weight to the new paradigm proposed by Kumar et al (2) to explain the pathophysiology of sepsis, where microbiologic

TABLE 4. Multivariate Analysis of Risk Factors for Hospital Mortality in All Patients ($n = 3,663$)

Factors	OR	95% CI	p
Source control[a]	0.809	0.658–0.994	0.044
Age[b]	1.017	1.011–1.023	< 0.001
Sex, female[c]	1.131	0.955–1.340	0.154
Acute Physiology and Chronic Health Evaluation II[b]	1.102	1.090–1.115	< 0.001
Septic shock[d]	1.338	1.108–1.616	0.002
Charlson comorbidity score[b]	1.067	1.029–1.106	< 0.001
Early broad-spectrum antibiotics	0.804	0.672–0.963	0.018
Fluids and vasopressors	0.863	0.733–1.014	0.074
Appropriate antibiotic therapy[e]	0.710	0.538–0.938	0.016
Nosocomial acquired infection[f]	1.971	1.610–2.414	< 0.001
Site of infection[g]			
Abdominal	0.952	0.758–1.196	0.671
Urologic	0.289	0.215–0.388	< 0.001
Central nervous system	1.179	0.683–2.036	0.554
Skin and soft-tissue	0.935	0.667–1.311	0.696
Others	1.073	0.779–1.478	0.664

[a]Compared with patients not requiring control.
[b]Per each point increase.
[c]Compared with male sex.
[d]Compared with severe sepsis.
[e]Compared with inappropriate antibiotic therapy.
[f]Compared with the emergency department.
[g]Compared with respiratory infection.

TABLE 5. Outcome Measurements in the Source Control Group

Outcome Measurements	All Patients Receiving Source Control, $n = 1,090$	Patients Receiving Source Control < 12 hr, $n = 825$	Patients Receiving Source Control ≥ 12 hr, $n = 265$	p
Duration of mechanical ventilation, d, mean (SD)	7.1 (13.1)	7.1 (12.9)	7.1 (13.9)	0.995
Duration of vasopressors, d, mean (SD)	4.8 (8.1)	4.6 (7.5)	5.4 (9.7)	0.168
ICU stay, d, mean (SD)	12.2 (15.3)	12.1 (15.2)	12.6 (15.4)	0.518
Hospital stay, days mean (SD)	32.3 (31.3)	31.9 (29.7)	31.6 (28.5)	0.884
Mortality, *n* (%)				
ICU	226 (20.7)	172 (20.8)	54 (20.4)	0.869
Hospital	299 (27.4)	228 (27.6)	71 (26.8)	0.789

load is the main driver of septic shock and rapid clearance of pathogens is central to outcome. This paradigm incorporates the concept of irreversible shock and suggests that the best approach to treatment is to minimize the time when a number of microorganisms sufficient to generate shock are present. Thus, early potent antimicrobial therapy and adequate source control are key components in sepsis management. Both crude and adjusted ICU mortality rates were lower in patients with source control; however, the decrease in hospital mortality was not evident until we adjusted for confounding factors. The hospital stay was longer in patients who required source control. One reason for this difference could be that abdominal infections were the most common source of sepsis in the source control group, and the definitive management of abdominal infections often requires more than one source control intervention, increasing morbidity, hospital stays, and

hospital mortality (18, 19). By contrast, in patients who did not require source control, the predominant source of sepsis was pneumonia, a less drainable focus. The lack of a drainable focus seems to be associated with worse outcome. One retrospective study that reviewed macroscopic findings in autopsies of 235 surgical ICU patients who died of sepsis or septic shock found a septic focus in approximately 80%, suggesting that the need for source control may be under recognized (20).

Although source control is essential to the successful management of severe sepsis and septic shock, in this observational database, we could not demonstrate that source control was time dependent. The SSC guidelines recommend that source control be undertaken within 12 hours of diagnosis (5), up from 6 hours in the previous guidelines. This increase was based on a recent retrospective study in 106 patients with septic shock and necrotizing soft-tissue infections where a delay of surgery more than 14 hours was independently associated with hospital mortality, but that study did not analyze other cutoff times (21). Although it is reasonable to assume that rapid source control is essential to maximize survival in severely septic patients with acute physiologic deterioration, scant evidence supports this approach. Only one study in patients with severe sepsis and septic shock showed a reduction (16%) in 28-day mortality when source control was performed within the first 6 hours, and this study only analyzed 234 of the 488 patients who needed source control (11). Several studies demonstrate the importance of early source control in necrotizing infections, but the definition of early source control varied between 2 and 24 hours (22–24). Another study in a large population of patients with fecal peritonitis found that early source control was not associated with better outcome (25). In our population, patients who received early source control also received better early resuscitation, suggesting that these patients might have been sicker; however, we found no significant differences in baseline characteristics between patients who received early source control and those who received late source control. Yet, despite better early management, the mortality for patients receiving early source control was similar to those receiving late source control. The most likely explanation is that the clinical team considered source control more urgent in patients who underwent earlier source control and that the multivariate analysis failed to measure this confounder. There are at least three reasons for delaying source control in severely septic patients: 1) small foci of infection might not be clinically evident at first; 2) physicians aware of the need for source control might delay intervention in apparently stable patients to enable nonemergency source control; or 3) surgical intervention might be deferred to allow necrosis to define itself anatomically to optimize intervention (e.g., in necrotizing pancreatitis) (26, 27). Determining the impact of early versus late source control would require formal randomization and prospective trials in more homogenous populations of patients and specific sources of infection (28).

This study has several limitations. We analyzed only patients who required admission to the ICU, possibly introducing a selection bias where patients with very early source control improve enough to avoid ICU admission. Although we adjusted for a number of predisposing patient factors, there may be other confounding factors that we did not measure. In addition, despite adherence to SSC guidelines as far as possible, many aspects of source control that we could not control (e.g., adequate preprocedure resuscitation) affect the outcome. Furthermore, we did not evaluate the type or the success of the source control measure; the specific source control technique and the technical success of the intervention can influence outcomes. A recent study in 44 ICUs found inadequate source control in 13.3% of patients with severe sepsis and septic shock (11), but percentages could be higher in necrotizing soft-tissue or abdominal infections. One study found that 64% of patients with necrotizing soft-tissue infections required more than one debridement (29), and another found that inadequate debridement was associated with increased mortality (22). Others found that failure to control the septic source in abdominal infections and the method used for source control affected outcomes (18, 30). Finally, this secondary analysis of an observational study has the weaknesses inherent to observational studies.

Our study has also strengths. We prospectively enrolled a large cohort of patients with severe sepsis and septic shock in a short time and monitored them until death or hospital discharge, resulting in a homogeneous database with high-quality control measures to ensure validity. Furthermore, the large number of ICUs participating means that the results can be extrapolated.

CONCLUSIONS

One third of patients with sepsis admitted to the ICU needed source control, especially those with abdominal and soft-tissue infections. Although patients who underwent source control were more severe and received worse initial resuscitation, their outcomes were better than those who did not undergo source control; these findings underline the importance of source control in the management of patients with severe sepsis or septic shock. We failed to demonstrate lower mortality for early source control versus late source control, but there is no rationale to defer source control in severe patients. Well-designed clinical trials including all patients with severe sepsis and septic shock, not just those admitted to the ICU, should examine the effects of early versus later source control in specific infectious foci. Educational and quality control programs are required to identify and control infectious foci in patients with severe sepsis and septic shock.

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