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Review

Importance of timely and adequate source control in sepsis and septic shock

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ABSTRACT

Source control is defined as the physical measures undertaken to eliminate the source of infection and control ongoing contamination, as well as restore anatomy and function at the site of infection. It is a key component of the management of patients with sepsis and septic shock and one of the main determinants of the outcome of infections that require source control. While not all infections may require source control, it should be considered in every patient presenting with sepsis; it is applicable and necessary in numerous infections, not only those occurring in the abdominal cavity. Although the biological rationale is clear, several aspects of source control remain under debate. The timing of source control may impact outcome; early source control is particularly relevant for patients with abdominal infections or necrotizing skin and soft tissue infections, as well as for those with more severe disease. Percutaneous procedures are increasingly used for source control; nevertheless, surgery—tailored to the patient and infection—remains a valid option for source control. For outcome optimization, adequate source control is more important than the strategy used. It should be acknowledged that source control interventions may often fail, posing a challenge in this setting. Thus, an individualized, multidisciplinary approach tailored to the infection and patient is preferable.

Introduction

Research has provided in-depth insight into the pathophysiology and management of sepsis and septic shock. Nevertheless, these conditions continue to pose a global health burden with consistently high morbidity and mortality rates.[1] Early diagnosis is key in the management of patients with sepsis and septic shock. This permits the provision of early and targeted therapy, with an emphasis on early, broad-spectrum antimicrobial therapy and supportive measures (e.g., restoration of tissue perfusion and initiation of organ support when necessary).[2,3]

In this context, source control is a cornerstone of sepsis management. Source control is defined as all physical actions that are used to eliminate the source of infection and control ongoing contamination.[4] These actions range from surgical interventions, such as laparotomy and percutaneous procedures, to the removal of infected devices. The aims of these efforts are to reduce the bacterial load at the site of infection, avoid the spread of infection beyond the primary site, and stop the progression of the dysregulated host response that defines sepsis.[5] The key components of source control include drainage, debridement, decompression, and definitive repair. Drainage refers to the evacuation of pus that has accumulated in abscesses or in body cavities, such as the peritoneum or pleural space. Debridement is the removal—often surgical—of necrotic, infected tissue or infected (prosthetic) devices. Decompression refers to reducing the pressure in one of the body cavities, typically the abdomen, where open abdomen treatment may be required to avoid intra-abdominal hypertension or abdominal compartment syndrome. Ultimately, source control also aims to restore premorbid anatomy and function. Nonetheless, this can be delayed until later stages, when patient physiology has recovered.

The importance of source control has been recognized for a long time, and its role in the pathophysiology is clear; however, the implementation of source control in contemporary clinical practice presents numerous challenges to healthcare professionals.[6] Several factors, such as optimal timing of source control, selection of the most appropriate intervention, and tailored follow-up after source control, may impact the effectiveness of source control and, therefore, patient outcomes.[7]

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Advances in diagnostic tools, evolving patient characteristics, improvements in supportive strategies, and the introduction of novel minimally invasive procedures have changed the paradigm of source control at the bedside. The aim of this article is to provide a comprehensive overview of the role of source control in sepsis and septic shock management, focusing on current concepts and controversies, clinical challenges, and future directions.

Understanding Sepsis and Septic Shock

Despite significant advances achieved in the use of antimicrobial agents and supportive measures, the pathophysiological mechanisms underlying sepsis have not been fully elucidated. An in-depth understanding is crucial for prioritizing therapies in patients presenting with severe disease. Sepsis and septic shock are caused by the body's dysregulated response to an infection.[8] It is estimated that 49 million new sepsis cases occur each year. These conditions are associated with disturbingly high mortality rates.[9] Hence, they are a health concern worldwide. Understanding the pathophysiological basis of these syndromes is crucial for successfully managing patients in the intensive care unit (ICU) and, ultimately, improving outcomes.

Sepsis has been defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[8] In practical terms, organ dysfunction is defined as an acute change in the Sequential Organ Failure Assessment (SOFA) score of two points or more, which is associated with a mortality rate >10%. Septic shock, occurring in a subset of patients with sepsis, is defined as persistent hypotension requiring the use of vasopressors to maintain a mean arterial pressure ≥65 mmHg, and serum lactate levels >2 mmol/L despite adequate volume administration. Septic shock is linked to a higher mortality rate than sepsis, with reported rates ranging from 30%–50%.[1]

The pathophysiology of sepsis and septic shock is complex; it involves a cascade of inflammatory and anti-inflammatory responses to the infection. Initially, the infection triggers an immune response that releases pro-inflammatory cytokines, such as tumor necrosis factor and interleukins. The aim of this inflammatory response is to control and eradicate the pathogen. However, in patients with sepsis, this host response becomes dysregulated and can cause systemic inflammation, further leading to organ dysfunction. In septic shock, this clinical condition is exacerbated with profound circulatory, cellular, and metabolic abnormalities. This dysregulated host response is also accompanied by coagulation impairment, which can lead to clinically important bleeding and even disseminated intravascular coagulation. These complications may have important implications for surgical intervention or other invasive procedures in patients.

Timely recognition and subsequent early intervention are the keys to managing patients with sepsis and septic shock.[2] Symptoms are caused by the infection (e.g., fever, tachycardia, and local symptoms depending on the site of infection) or related to organ dysfunction (e.g., altered mentation, breathing difficulty, and reduced diuresis), reflecting the systemic nature of the illness.[10] Early diagnosis of sepsis is crucial for avoiding poor outcomes. It allows for timely treatment, which typically includes antimicrobial therapy, source control, and supportive care (fluid resuscitation and, when necessary, vasopressors and organ support). Of note, prevention and early detection of patients with developing sepsis is currently the best available strategy. Early detection allows for early therapy, which may avoid the deterioration of infection to sepsis and eventually septic shock.

Importance of Source Control in Managing Patients with Sepsis and Septic Shock

Source control represents a key element in the management of sepsis and septic shock. Its importance cannot be underestimated in infections that require removal of the focus of infection to improve treatment effectiveness.[4] Source control involves the identification and removal of the infection source to halt the ongoing microbial contamination of a normally sterile organ, tissue, or body cavity.

While source control is typically associated with abdominal infections, it is also relevant for several organ systems.[5] Infections occurring in the nervous system (e.g., brain abscesses, ventriculitis, or epidural abscesses) require drainage and, occasionally, decompression. In the chest, infections such as empyema, mediastinitis, or sternitis often require source control. The principles of source control can also apply to numerous infections occurring in the genitourinary tract and organs. Catheter-associated bladder infections require removal of the catheter; in case of obstructive pyelonephritis, decompression is required; and drainage is necessary for kidney or pelvic abscesses. Infective endocarditis may require debridement and resection of the native valve, followed by valve replacement; drainage is required for infective pericarditis. The management of several infections in the abdomen requires source control. In the case of cholangitis, any obstruction must be removed, while solid organ abscesses (e.g., spleen or liver) should be primarily drained percutaneously. Infected pancreatic necrosis is a more challenging infection; percutaneous or surgical minimally invasive drainage and debridement may be needed depending on the stage, location, and extent of infection. Finally, drainage is required for necrotizing skin and soft tissue infections (e.g., necrotizing fasciitis [11] or postoperative surgical site infections); in case of necrosis, debridement is also required. Based on these examples, it is evident that source control is applicable to many infections and, therefore, should be considered in each patient presenting with sepsis and septic shock.

The rationale behind source control is straightforward: the systemic inflammatory response provoked by the infection can be halted or diminished by directly eliminating the source of infection. Source control effectively reduces the bacterial load at the infection site, thereby assisting in the control and killing of any remaining pathogens by the body's immune response and antimicrobial therapy.

Many studies have investigated the importance of source control and its impact on patient outcomes. The recent European Society of Intensive Care Medicine-endorsed Abdominal Sepsis (ABSES) Study: Epidemiology of Etiology and Outcome study found that patients treated for intra-abdominal infection who did not achieve source control within 7 days were associated with an increased risk of death.[12] Patients who did not achieve source control and required additional interventions had a 1.9-fold higher probability of dying *vs.* other patients. Notably, those in whom source control was not achieved and had persistent signs of inflammation were linked to an almost 5-fold higher probability of mortality compared with other patients. In this context, it is also important to note that adequate source control is required for effective antimicrobial therapy. Among patients presenting with septic shock due to a fungal infection, investigators found that antimicrobial therapy was ineffective in those with an uncontrolled source of infection.[13] In cases with adequate source control, patients who also received adequate antifungal therapy had a higher chance of survival *vs.* others. Therefore, it appears that source control addresses the root cause of the problem rather than merely treating the symptoms of sepsis and septic shock. Moreover, studies have revealed that source control plays an important role in improving outcomes in patients with bloodstream infections. Notably, mortality was higher in patients who required source control but did not achieve it.[14] According to the available evidence, source control is required for effective antimicrobial therapy. Therefore, source control can be considered the basis of sepsis management in the sepsis pyramid (Figure 1).

Effective source control is also needed to avoid the development of antimicrobial resistance. Lack of source control often implies prolonged antimicrobial therapy, which is a key driver of antimicrobial resistance. Changes in the intestinal flora after treatment with antimicrobials facilitate colonization and subsequent infections with resistant pathogens, leading to prolonged, persistent tertiary peritonitis. This process is associated with poor healing of bowel injuries, resulting in a vicious cycle.

Based on the above evidence, source control is a critical element for achieving clinical success in patients with sepsis or septic shock caused by infections that require effective control of the source of infection. The outcome is determined by three important aspects of source control, which should be carefully considered: (1) the timing of the source control intervention; (2) the strategy used to achieve source control; and (3) the adequacy of the source control procedure in terms of complete removal of the source of infection and any ongoing contamination. These aspects are discussed in detail.

Timing of Source Control

A growing body of evidence supports the importance of early source control. Generally, the consensus among clinicians and researchers is that timely control of the source of infection is associated with a better prognosis. However, the exact timing and its implementation in clinical practice present challenges that warrant in-depth discussion.

The Surviving Sepsis Campaign guidelines recommend that source control measures are implemented within 12 h after diagnosis.[2] This recommendation is based on several studies showing that delays in source control are associated with increased mortality rates. Table 1 summarizes recent studies that have examined the relationship between the timing of interventions and outcomes in patients with sepsis and septic shock. Notably, investigations reported in the literature involved different types of infections, settings, and patients. Consequently, a comparison between different studies is challenging. From a pathophysiological point of view, there is no reason to assume that there is a certain cut-off point beyond which the timing of source control no longer plays a role.

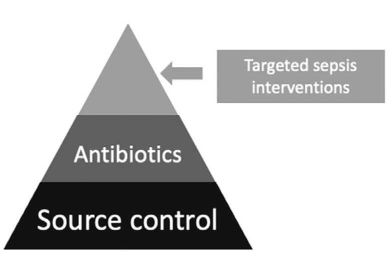

Figure 1. The sepsis pyramid.

The ABSES study showed that urgent source control was the only modifiable factor associated with lower odds of mortality.[15] A Korean multicenter study involving patients with septic shock presenting to the emergency department investigated different sources of infection. The researchers found that delayed source control beyond 6 h after presentation was not associated with mortality at day 28.[16] Furthermore, extending the time frame up to 12 h did not result in an increased mortality rate. It is noteworthy that almost half of the infections were of hepatobiliary origin, and most patients were treated with percutaneous catheter drainage. In a more recent study from France on patients with community-acquired intra-abdominal infection requiring surgery (with mild illness), each hour of delay was linked to a 2% increase in the mortality rate.[17] Other risk factors associated with poor outcomes in this study included the severity of disease and generalized peritonitis. The Medical Education for Sepsis Source Control and Antibiotics study group reported that among >1500 patients who required source control delays of >6 h significantly increased the mortality rate.[18] Notably, this relationship was observed only in patients with septic shock. Following adjustment for confounders, patients with less severe disease had similar outcomes irrespective of the timing of the procedure. In another study involving almost 5000 patients with community-acquired sepsis from 14 hospitals in the USA, the average time to source control was 15 h; in 27% of the patients, source control was obtained within 6 h.[19] Overall, the mortality rate was reduced in patients in whom the source was controlled early (i.e., ≤6 h). Sensitivity analysis demonstrated that patients with higher scores for disease severity and those with infections arising from the gastrointestinal tract or occurring in the abdomen, as well as soft tissue infections, benefited most from early surgery. Further investigation revealed a linear increase in the risk-adjusted mortality rate in patients undergoing explorative laparotomy or soft tissue debridement, however, this relationship was not observed in patients treated with drainage.

From a practical point of view, the urgency of source control is determined by three factors: (1) the presence and magnitude of ongoing contamination, (2) the degree of organ dysfunction, and (3) patient physiology at presentation. Based on these characteristics, patients can be classified into three categories according to the degree of urgency for source control.[4] For patients in category 1, source control is required as soon as possible (i.e., suspicion of sepsis or confirmation of diagnosis). Any delay in source control in these patients is associated with an increased risk of mortality. Examples include necrotizing skin and soft tissue infections, intra-abdominal infections (particularly in cases characterized by rapid deterioration of organ dysfunction), or abdominal compartment syndrome. In these patients, fluid resuscitation should be promptly performed and continued dur-

Table 1
Overview of selected recent studies investigating the impact of the timing of source control procedures in patients with sepsis and septic shock.

First author	Population	Definition of early source control	Impact on mortality
De Pascale G[15]	Patients in the ICU with intra-abdominal infection (n=1077)	2–6 h	Early source control: OR=0.50, 95% CI: 0.34 to 0.73
Reitz KM[19]	Community-acquired sepsis requiring source control (n=4962)	<6 h	Early source control: aOR=0.71, 95% CI: 0.63 to 0.80
Rüddel H[18]	ICU patients with sepsis requiring surgical source control (n=1595)	NA	All patients: aOR=1.008, 95% CI: 0.997 to 1.02 per hour delay Septic shock patients only: aOR=1.013, 95% CI: 1.001 to 1.026 per hour delay
Boyd-Carson H[29]	Patients requiring emergency laparotomy for perforated peptic ulcer (n=3809)	NA	aOR=1.04, 95% CI: 1.02 to 1.07 per hour delay Shocked patients aOR=1.06, 95% CI: 1.01 to 1.11 per hour delay;
Karvellas CJ[30]	Patients with cholecystitis associated septic shock (n=196)	<16 h	Delayed source control: OR=4.45, 95% CI: 1.88 to 10.70
Kim H[16]	Patients with septic shock visiting the ED (n=524)	<6 h	Delayed source control: aOR=1.418, 95% CI: 0.724 to 2.779
Martínez ML[31]	Patients with sepsis or septic shock admitted to the ICU (n=1090)	<12 h	Delayed source control: OR=1.082, 95% CI: 0.756 to 1.548

aOR: Adjusted odds ratio; CI: Confidence interval; ED: Emergency department; ICU: Intensive care unit; NA: Not available; OR: Odds ratio.

ing the source control procedure. For patients in category 2, source control is required as soon as their physiology permits intervention. Although these patients may appear stable, there is some time for correction of metabolic disorders; it is important to implement source control interventions as soon as possible. The timing of source control may also be determined by the availability of an experienced operator or the operating room. Examples include patients with secondary peritonitis, pleural empyema, and acute cholecystitis. Most patients are classified into this category. Finally, for patients in category 3, source control is required once the process of infection has been demarcated. A typical example is infected pancreatic necrosis in clinically stable patients. Delaying a percutaneous intervention or surgical procedure makes the procedure easier and causes less collateral damage.

Clinicians should be aware that there are many obstacles to early source control. These obstacles may be related to the diagnostic process or the infrastructure. A lack of clinical symptoms, the presence of concomitant infections, the perceived need for more technical investigations, such as computed tomography (CT) scanning, as well as access to radiology, may delay the diagnosis of an infection that requires source control. As mentioned, the availability of interventional radiology or surgery depending on the preferred intervention for source control may also impact the timing of source control. In many hospitals, the availability of operating theaters can be limited. Moreover, for some infections, the unavailability of an experienced surgeon (e.g., endocarditis) may preclude early surgery.

However, the urgency of source control must be balanced with the physiological status of the patient. For instance, performing surgery on a hemodynamically unstable patient may further worsen their condition, resulting in adverse outcomes despite timely source control. In such scenarios, initial resuscitation to stabilize the condition may be required before proceeding with invasive source control measures, although resuscitation and source control can be simultaneously performed in many instances.

The optimal timing can also be influenced by the nature and location of the infection. For example, while early drainage of an accessible abscess may be straightforward, controlling a deep-seated or endovascular infection may necessitate a more careful, staged approach by experienced physicians. Furthermore, source control may not been achieved with a single intervention in all cases. Ongoing monitoring and reassessment are crucial, as additional interventions may be necessary. Therefore, the notion of “time to source control” should be considered a dynamic rather than a static concept.

A key challenge in implementing early source control is the need for rapid detection of the infection type and location, including the need for source control. The identification of sepsis, determination of the infection source, and planning of the appropriate source control measures may require multidisciplinary discussion and, therefore, may be a time-consuming process. This challenge underscores the importance of maintaining a high index of suspicion for sepsis and utilizing rapid diagnostic technologies, including ultrasound and CT, to identify sources of infection amenable to source control.

Source Control Strategies

In the past decades, there have been significant advances in modalities used to control a source of infection. For some infections, e.g., catheter-related infections, the removal of the infected catheter is a straightforward process. Nevertheless, it is more complex for the majority of infections, thereby complicating clinical decision-making. There are two main strategies available, namely, surgical drainage and percutaneous drainage. Previously, surgical drainage was the standard for the bulk of infections. However, the development of percutaneous drainage (especially the availability of ultrasound and CT) has completely altered the approach to source control.[20,21] Percutaneous drainage has become the primary choice for numerous infections, including postoperative abscesses, visceral abscesses in different locations, etc. It can be easily performed bedside under ultrasound guidance in many clinical situations. However, surgical drainage remains an option in several situations. Especially for patients with intra-abdominal infections with ongoing contamination or diffuse peritonitis, surgery is considered the treatment of choice. Additionally, surgery may be preferred in case of associated necrosis.

According to the literature, the spectrum of source control interventions has changed substantially. A Korean multicenter study on source control revealed that up to two-thirds of the patients were treated with percutaneous catheter drainage or endoscopic intervention.[16] Only 20% of patients required a surgical procedure; in the remaining patients, infected devices were removed. It is difficult to conclude whether percutaneous drainage is better than open surgery. Of note, most studies conducted thus far did not sufficiently adjust for confounders; a study comparing open surgery *vs.* percutaneous drainage found a 2-fold higher mortality rate in patients treated with the former option. Nevertheless, it is highly likely that selection bias was present in this study.[22]

From a clinical perspective, it appears sensible that collateral damage should be avoided at all times, while concurrently pursuing complete source control. The most suitable strategy may be decided based on patient characteristics and available resources in the hospital. Determinants may include the hemodynamic stability of the patient, the presence of coagulation disorders, intrabdominal pressure in case of intra-abdominal infections, prior surgery, etc. The availability of expertise for percutaneous procedures or surgical intervention may also influence the selection of source control strategy. Timely and adequate definitive containment of bacterial contamination is the priority. Nonetheless, it is often challenging to determine the most appropriate source control strategy for an individual patient at a particular moment in time. Some patients may benefit from an initial prudent approach, which includes drainage only, followed by extensive control of the contamination and restoration of anatomical defects. In contrast, in other cases, an immediate and meticulous removal of infection may be the best option. The success of various interventions may also depend on the location of the infection, the clinical phenotype, or the physiological status of the patient. New tools, such as rapid diagnostics, innovative biomarkers or omics, or artificial intelligence, may assist us in the future to make informed decisions in this domain.

Adequacy of Source Control

The timing of source control and the preferred strategy attract considerable research attention with regard to source control. However, the adequacy of the procedure is probably an equally important aspect. Evidence has shown that source control is not successful in all cases. In the ABSES study, almost half of the patients did not achieve source control from the first attempts; thus, many patients required additional procedures.[12] van de Groep et al.[23] performed another multicenter study in patients with sepsis requiring a source control procedure for an intra-abdominal infection. They found that both surgical and percutaneous source control procedures were often unsuccessful; multiple procedures were needed, with a proportion of patients undergoing up to seven interventions. When evaluated at day 14, only 40% of the patients had adequate source control; source control was considered delayed but adequate in approximately 30%, and inadequate in the remaining 30%. Strikingly, immediate procedural adequacy was estimated at >90% in all patients. Other studies have corroborated these findings, indicating that source control is often inadequate. Clinicians should be aware of the high risk of failed source control. Unfortunately, the detection of inadequate source control is difficult. In a study on intra-abdominal infections, white blood cell count, C-reactive protein levels, or the presence of fever were unable to discriminate between patients with inadequate *vs.* adequate source control.[23] The SOFA score was the only potentially helpful tool; persistently elevated SOFA scores were suggestive of inadequate source control. Evidence from a small study suggested that procalcitonin could be helpful in this context [24]; nevertheless, confirmation of these findings in larger studies is required. C-reactive protein and other biomarkers may play a role in identifying patients with organ—space surgical site infections after elective colorectal surgery.[25,26] However, these data may not be readily extrapolatable to patients with failed source control in the ICU. In patients with uncontrolled sepsis, a complex balance between inflammation and anti-inflammatory responses may lead to prolonged dysfunction of multiple organs, and the use of biomarkers to detect failed source control may be challenging.[27] A clinical approach combining clinical evaluation, biomarkers, and targeted imaging is the most appropriate option. In case abdominal drains are present, such drains can also be helpful in determining the source control, although this approach is not specific to this diagnosis.[28]

Future Directions

Based on the current knowledge and available evidence, several aspects of sepsis warrant further investigation. Notably, personalized medicine approaches, based on genetic and phenotypic profiling, could revolutionize sepsis management. Such approaches include the identification of patients who may benefit from source control at a certain point in time and the most appropriate type of intervention for each case. Moreover, there is an urgent need to define the critical time frame for establishing source control for different infections. With the advent of less invasive strategies for source control, there may be an opportunity to minimize the use of more invasive interventions associated with higher perioperative risks. Although conceptually attractive, the application of temporizing strategies has not resulted in any benefits, and guidance is clearly needed. Retrospective data may be useful, but confounding by indication may be difficult to overcome. As decision-making is often complex and challenging, a multidisciplinary approach to source control is a logical next step. However, this concept has not been adequately investigated thus far. Such an approach may shorten the time to source control and improve outcomes, as more informed choices are made. Finally, research into patient factors that impact outcomes and the role of the intricate interaction between antimicrobial therapy choices and source control to maximize the effect of both treatment pillars is imperative. These under-researched areas should be at the forefront of future investigations to fill the existing gaps and lead to advancements in source control for sepsis.

Conclusions

Early source control is a cornerstone of comprehensive sepsis management, and its execution requires careful clinical judgment. Source control is applicable to a wide array of infections; therefore, each patient presenting with sepsis or septic shock should be assessed for the need for source control. The timing of source control remains a controversial issue. While it is not advisable to delay source control once the indication has been established, patients with abdominalor necrotising skin, and soft tissue infections appear to benefit most from prompt source control. Percutaneous drainage and surgical intervention remain valid options, depending on the focus and extent of the infectious process, the presence of any necrosis, and ongoing contamination of a sterile body site. Finally, the adequacy of source control is an important aspect, with failed source control being more frequent than expected. Source control should be seamlessly integrated with other management strategies. A patient-centered, multidisciplinary approach with the involvement of intensivists, surgeons, infectious disease specialists, radiologists, and nurses is vital to guide this complex process.

Author Contributions

Jan J. De Waele: Writing – review & editing, Writing – original draft, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

Jan De Waele has served as a consultant for Menarini, MSD, Pfizer, ThermoFisher, and Viatris (fees and honoraria paid to the institution).

Data Availability

Not applicable.

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