Source control - often needed, often difficult

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Transparency declaration

Speakers /advisory board honoraria

PFIZER, MSD, ASTELLAS
Introduction

• Early empiric therapy and adequate resuscitation have been identified as main predictors of outcome in patients with candidemia or bacteremia.

• Source control is an additional major determinant of outcome as a measure to reduce microbial burden.

• The need of prompt source control (within 12 hours) has been emphasized in the most recent Surviving Sepsis Campaign (SSC)
  • (within 12 hours after diagnosis [grade 1C, SSC 2012])

What is source control?

• Source control measures include all those actions taken in the process of care to control the foci of infection and to restore optimal function of the site of infection

• Intraabdominal (IAI) along with skin and soft tissue infections (SSSI) are the sites where a rapid source control seems more feasible

• Other infections where it may apply are implant-associated infections, catheter-related infections, urinary infections, thoracic infections etc.

What is source control?

• drainage of infected fluid collections;
• debridement of infected solid tissue;
• removal of devices or foreign bodies;
• definitive measures to correct anatomic derangements resulting in ongoing microbial contamination and restore optimal function

Source control’s effectiveness depends on the infection site, the patient’s premorbid state, and the resources available


Jimenez MF et al, Care Med 2001;27 Suppl 1:S49-62
Is source control a modern approach?

Ancient Egyptian-Roman-Greek Surgeons

No! It is an ancient one

Drainage of abscesses
Amputations
Abdominal surgery
Wound dressings
War trauma!
Skin and soft tissue infections

• Necrotizing soft tissue infections (NSTIs) are almost always complicated by severe sepsis or septic shock
• The value of source control EXTREMELY important
• Other severe SSTIs are responsible for about 10% of all cases of septic shock [after pneumonia (55-60%) and abdominal infections (25%)]
• In Randomised controlled trials 4-8% of cSSSIs are associated with septic shock
• The worldwide average mortality of severe SSTIs is around 30%

Shen HN, BMC Infect Dis 2010; 10:151
Source control actions relating to skin and soft tissue infections

- Device removal
- Incision and drainage
- Limited debridement for maximum preservation of vital tissue
- Extended debridement for removal of all infected and necrotic tissue
- Amputation
## Aspects of source control in severe soft tissue infections

<table>
<thead>
<tr>
<th>(Surgical) measure</th>
<th>Clinical setting</th>
<th>Example(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device removal</td>
<td>Superficial or deep-seated infected device</td>
<td>Infected central venous catheter-infected vascular graft</td>
</tr>
<tr>
<td>Incision and drainage</td>
<td>Abscess formation</td>
<td>Perineal abscess deep surgical-site infection</td>
</tr>
<tr>
<td>Limited debridement</td>
<td>Limited local extent of infection</td>
<td>Diabetic foot infection</td>
</tr>
<tr>
<td>Radical debridement</td>
<td>Necrotizing soft tissue infections with severe sepsis</td>
<td>Necrotizing fasciitis Fournier’s gangrene</td>
</tr>
<tr>
<td>Amputation</td>
<td>Infected necrosis of the extremities</td>
<td>Gas gangrene</td>
</tr>
</tbody>
</table>

Eckmann C, Curr Opin Infect Dis 2016, 29:139–144
Early and late signs and symptoms of severe skin and soft tissue infections.

**Early symptoms**
- Pain out of proportion
- Fast progression
- Erythema
- Edema
- High tissue tension

**Late symptoms**
- Skin necrosis
- Blackish bullae
- Crepitatio
- Mental disorientation
- Organ failure
- Septic shock
Time is crucial for source control in necrotizing SSIs!

• Full blown disease is difficult to be mis-diagnosed
• Nevertheless, early signs and symptoms are mainly insignificant
• In uncertain cases, a deep diagnostic testing incision right down to the fascia is the most rapid diagnostic procedure
• Once NSTI is confirmed, a radical debridement should follow, otherwise secondary closure can be aimed for

Diagnostic approach in severe skin and soft tissue infections

NTSIs:
- Solid evidence for radical debridement
- Only one study reported conservative approach in NTSIs
- Repetitive debridements may be required
- A planned re-debridment at 24 hours is important


Eckmann C, Curr Opin Infect Dis 2016, 29:139–144
Timing of source control in SSTIs

Non-necrotizing

• The adequate timing of minor source control measures in non-NSTIs has never been investigated

• Source control within 24 h after admission is recommended but this has never been proven in clinical trials

Necrotizing

• Prognosis in NSTI has always been presumed to be dependent on the time of first surgical intervention.

• A delayed surgical intervention (more than 24 h after admission) portends increased mortality
Timing of source control in NTSIs

- Studies focusing on patients with type I (mixed infection with aerobic and anaerobic bacteria) or type II (group A β-hemolytic streptococcus, Staphylococcus aureus) Necrotizing Fasciitis found that patients who had less than a 14- to 36-hour interval between admission and surgical debridement vs those receiving surgical debridement less than 7 days after the onset of initial symptoms could have a better prognosis.

- Delayed surgical treatment is associated with more surgical debridements and mortality

- Complex trade-off between operating too early, when patients may not be stable enough to be moved to the operating room, and operating too late, when patients have little chance of survival

Kobayashi L, J Trauma 2011;71:1400-5

The golden rule of 12 hours after admission to initiate surgical treatment

• In a retrospective study of 121 patients with *Vibrio vulnificus*–related NF, a substantial reduction in mortality risk was achieved by initiating surgical treatment within 12 hours after admission compared with delaying either 12 to 24 hours or more than 24 hours after admission to initiate surgical treatment.

• there was no difference in mortality risk between the latter 2 groups.

The golden rule of 12 hours after admission to initiate surgical treatment

• The therapeutic benefit of surgical treatment within 12 hours of admission is approximately 515 lives per 1,000 persons treated (adjusted NNT 5 1.94) when the therapeutic effect of surgical treatment more than 24 hours after admission was assumed to be zero.

• Surgical delays might have resulted from managing the patient’s unstable condition.

ANTIBIOTIC THERAPY
Necrotizing SSIs

• Large randomized trials are not available because of disease rarity
• A polymicrobial spectrum is usually involved
• The administration of clindamycin is recommended to inhibit exotoxin production of Gram-positive bacteria
• Treatment duration can usually be limited to 8–10 days

Adjunctive therapies for Necrotizing SSIs
Hyperbaric Oxygen

- Theoretic Background: by raising the plasma oxygen pressure a bacteriostatic effect directed towards *Clostridium* spp is achieved through blocking clostridial *α*-toxin.
- The value of HBO in the treatment of severe, especially NSTIs, is yet not validated.
- In a review of several studies, a reduction of debridement could be achieved using HBO, although overall patient mortality was not affected.
- In other cohorts, a survival benefit was found.
- Recently, a large US database of patients with NSTI with more than 50,000 patients, there was no advantage in morbidity and mortality for those patients who had received HBO.

Adjunctive therapies for Necrotizing SSIs

Intravenous immunoglobulin

- Immunoglobulins in the treatment of severe SSTIs has not been investigated in clinical trials
- Case reports and case series
- The administration of intravenous immunoglobulin in patients with streptococcal toxic shock syndrome with or without necrotizing fasciitis has been controversial
- Critically ill patients with haemodynamic instability might benefit from diminishing hyperinflammation by immunoglobulins

Source control recommendations for Necrotizing Skin and Soft tissue infections

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Prompt and extensive surgery</th>
<th>Second re-debridement</th>
<th>Broad spectrum antibiotics</th>
<th>IVIG</th>
<th>HBO</th>
<th>VAC</th>
<th>Diverting ostomy for Fournier gangrene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevens IDSA Guidelines</td>
<td>2014</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sartelli (WSES guidelines)</td>
<td>2014</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Misiakos (review)</td>
<td>2014</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

++ highly recommended, + to be considered individually, - measure not mentioned

HBO: hyperbaric oxygen, IVIG: intravenous immunoglobulin, VAC: vacuum-assisted closure

Eckmann C, Curr Opin Infect Dis 2016, 29:139–144
Source control in SSSIs

Summary

• Risk assessment includes estimation of causative agents, clinical picture, depth of invasion as well as local and systemic progression.
• Easy to perform measures such as device removal, limited debridement or simple opening and drainage of an abscess can be successful.
• The more severe the soft tissue infection is, the more aggressive the approach to source control should be.
• In necrotizing SSTIs, patients after a short clinical diagnostic workup require radical debridements and redebridement for control of the infection.
• The key to successful treatment of severe soft tissue infections is based on early detection, immediate adequate antibiotic treatment and prompt and radical surgical debridement.
Intraabdominal infections (IAIs)
IAIs and source control

- IAIs are the second cause of admission to the ICU
- Increasing trend of nosocomial IAIs requiring ICU admission due to organ failure
- Source control actions are feasible and of proven clinical benefit

Innui T, Surgery 2009;146:654-61; discussion 661-2

Vincent JL, JAMA 2009;302:2323-9
Intraabdominal infections (IAIs) and source control

• Time between admission and source control in IAI has been assessed as a critical determinant of survival in patients with GI perforation with associated septic shock and in some intra-abdominal candidiasis cases
• “early” denotes a range from 2 hours up to 5 days
• The quality of source control is difficult to evaluate
• Without source control IAIs portend a mortality up to 100%

Tellor B, Surg Infect (Larchmt) 2015;16:785-93
Source control actions relating to intra-abdominal infectious foci

• Prevention in the surgical incision
• Drainage of abscesses
• Debridement of infected necrotic tissues
• Removal of potential infected devices
• Extensive intra-abdominal cleansing to reduce peritoneal bacterial inoculum
• Second time abdominal wall closure

Patients with IAI may be not eligible for major surgery

• Non-severe cases, localized abscesses and high risk patients (in septic shock with high doses of inotropes or requiring other supportive measures) could benefit from minimally invasive procedures including percutaneous and endoscopic approaches

• Recent recommendations on source control and peritonitis use the term “damage control” surgery for this kind of critically ill patients

What is the current evidence in IAI?

• A recent study in 44 ICUs found inadequate source control in 13.3% of patients with severe sepsis and septic shock, 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.

• Failure to control the septic source in abdominal infections affected outcomes.

• In some studies the method used for source control impacted on outcomes.

As early as possible? Where is the cut-off?

- **<6 hours?** 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.

- **<24 hours?** 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.

- **<12 hours?** 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, was the driver of the recent recommendation; however, that study did not analyze other cut-off times.

Kobayashi L, J Trauma 2011; 71:1400–1405
Bloos F, Crit Care 2014; 18:R42
Impact of Source Control in Patients With Severe Sepsis and Septic Shock*

María Luisa Martínez, MD¹; Ricard Ferrer, MD, PhD²,³; Eva Torrents, MD¹; Raquel Guillamat-Prats, PhD³; Gemma Gomà, RN¹; David Suárez, MSc, PhD⁴; Luis Álvarez-Rocha, MD⁵; Juan Carlos Pozo Ladero, MD, PhD⁶; Ignacio Martín-Loeches, MD, PhD⁷; Mitchell M. Levy, MD, FCCP, FCCM⁸; Antonio Artigas, MD, PhD⁹; for the Edusepsis Study Group

• Prospective observational analysis of Spanish national multicenter educational intervention to improve antibiotherapy in sepsis.
• Setting: Ninety-nine medical-surgical ICUs in Spain.
• Patients: 3,663 patients with severe sepsis or septic shock
• A total of 1,173 patients (32%) underwent source control, predominantly for abdominal, urinary, and soft-tissue infections.
• 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 requiring source control a 3.5 fold had an abdominal cause of sepsis.

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).

Source control after 12 hours was not associated with higher mortality (27.6% vs 26.8%; p = 0.789).
## Outcome Measurements in the Source Control Group

*Crit Care Med 2017; 45:11–19*

<table>
<thead>
<tr>
<th>Outcome Measurements</th>
<th>All Patients Receiving Source Control, ( n = 1,090 )</th>
<th>Patients Receiving Source Control &lt; 12 hr, ( n = 825 )</th>
<th>Patients Receiving Source Control ≥ 12 hr, ( n = 265 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of mechanical ventilation, d, mean (sd)</td>
<td>7.1 (13.1)</td>
<td>7.1 (12.9)</td>
<td>7.1 (13.9)</td>
<td>0.995</td>
</tr>
<tr>
<td>Duration of vasopressors, d, mean (sd)</td>
<td>4.8 (8.1)</td>
<td>4.6 (7.5)</td>
<td>5.4 (9.7)</td>
<td>0.168</td>
</tr>
<tr>
<td>ICU stay, d, mean (SD)</td>
<td>12.2 (15.3)</td>
<td>12.1 (15.2)</td>
<td>12.6 (15.4)</td>
<td>0.518</td>
</tr>
<tr>
<td>Hospital stay, days mean (SD)</td>
<td>32.3 (31.3)</td>
<td>31.9 (29.7)</td>
<td>31.6 (28.5)</td>
<td>0.884</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality, n (%)</th>
<th>ICU</th>
<th>ICU</th>
<th>ICU</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>226 (20.7)</td>
<td>172 (20.8)</td>
<td>54 (20.4)</td>
<td>0.869</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>299 (27.4)</td>
<td>228 (27.6)</td>
<td>0.789</td>
</tr>
</tbody>
</table>

**Conclusion:** Never say “it is too late for source control”!
What about source control in IA candidiasis?
Retrospective cohort study in Spanish ICUs
Mortality was higher in the ICU group compared to what was documented for the non-ICU group (35% vs 19.5%, p = 0.011).
Adequate source control within 48 h of diagnosis was achieved in 60% of the cohort.

- The population receiving both adequate source control and adequate antifungal treatment was the one associated with a higher survival rate, in both the ICU and surgical wards.
- Source control remains the main goal for decreasing mortality of IAC episodes inside and outside the ICU.
Is source control efficient in the era of Carbapenem-resistant pathogens?

Probably more efficacious than other measures i.e. early adequate antimicrobial treatment
• Matched case control study
• 99+99 patients with CR-KP
• 27 patients with catheter associated bacteremia
• 34 patients with intraabdominal infection (14 of them bacteremic)
• Removal of the focus of infection (catheter removal, abscess drainage, wound debridement) was independently associated with survival ($P \leq 0.002$).
• The overall in-hospital mortality was 48%.
• 42 patients with CR-KP BSI
• Retrospective study
• 42% crude 30 day mortality

**Multivariate analyses**

<table>
<thead>
<tr>
<th>Potential source(s) of infection and adjunctive procedures performed, n (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of CVC</td>
<td>41 (85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVC removed within 5 days of first positive blood culture</td>
<td>25 (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of Foley catheter and positive urine culture</td>
<td>13 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foley removed within 5 days of first positive blood culture</td>
<td>6 (46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of positive wound/abscess culture</td>
<td>15 (31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound/abscess drained/debrided within 5 days of first positive blood culture</td>
<td>11 (73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>30-day mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of eradication from blood culture at 7 days</td>
<td>35</td>
<td>6–204.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Microbiologic eradication at 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>36.2</td>
<td>2.6–510</td>
<td>.008</td>
</tr>
<tr>
<td>mAPACHE II</td>
<td>0.746</td>
<td>0.58–0.96</td>
<td>.021</td>
</tr>
<tr>
<td><strong>Favorable response at 7 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of source control</td>
<td>12.2</td>
<td>1.4–110</td>
<td>.025</td>
</tr>
<tr>
<td>Eradication from blood culture at 7 days</td>
<td>5.5</td>
<td>0.96–31.5</td>
<td>.056</td>
</tr>
</tbody>
</table>
• Retrospective analysis of 111 patients with septic shock by KP-KPC
• 30d mortality 39.4%, Colistin resistance 51.3%

**Table 3.** Cox regression analysis of factors associated with death

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>HR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin-containing antibiotic regimen</td>
<td>0.21</td>
<td>0.05-0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Two or more <em>in vitro</em> active antibiotics as definitive therapy</td>
<td>0.08</td>
<td>0.02-0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Control of removable source of infection</strong></td>
<td><strong>0.14</strong></td>
<td><strong>0.04-0.25</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Colistin-resistant strain</td>
<td>8.09</td>
<td>3.14-11.23</td>
<td>0.001</td>
</tr>
<tr>
<td>Intra-abdominal source of infection</td>
<td>2.92</td>
<td>2.11-4.12</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Legend.** KPC-Kp: *Klebsiella pneumoniae* carbapenem-resistant; ICU: intensive care unit.
Conclusions

• Source control has received less attention than other treatments in the Surviving Sepsis Campaign

• Source control in high risk patients even beyond the 12 hour time-frame from admission is associated with improved outcomes

• Source control along with early antifungal treatment is associated with improved survival in intraabdominal candidiasis

• The quality and adequacy of source control are not clearly delineated—minimally invasive approaches need to be evaluated vs classic surgery in prospective studies

• Source control may prove extremely important in infections by MDR pathogens
Thank you for your attention

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