GIORNATA MONDIALE DELLA SEPSI

DIAGNOSI E GESTIONE CLINICA DELLA SEPSI
Giovedì, 13 settembre 2018

Sepsi: nuove definizioni, approccio diagnostico e terapia

Nicola Petrosillo

Società Italiana Terapia Antiinfettiva (SITA)

Istituto Nazionale per le Malattie Infettive "Lazzaro Spallanzani", IRCCS-Roma

Sepsis: a never-ending story

- Although common and associated with high morbidity and mortality, sepsis and related terms remain difficult to define.
- Two international consensus conferences in 1991 and 2001 used expert opinion to generate sepsis definitions.
- However, advances in the understanding of the pathobiology and appreciation that elements of the definitions may be outdated, inaccurate, or confusing prompted the European Society of Intensive Care Medicine and the Society of Critical Care Medicine to convene a Third International Consensus Task Force to reexamine the definitions.
- This is sepsis-3

Bone RC et al. Chest 1992; 101:1644–1655
Levy MM et al. Crit Care Med 2003; 31: 1250-56
Singer M et al. JAMA 2016; 315: 801–8

- **SEPSIS-3 has solved a major problem of SEPSIS-2, which required the presence of systemic inflammatory response syndrome (SIRS) + suspected infection to define sepsis.**

- **For most physicians, the term “sepsis” is usually reserved for patients with a severe infection deserving critical care.**

- **Using the SEPSIS-2 criteria would “overestimate” the number of cases of this disease by considering uncomplicated infection as sepsis.**

- **Conversely, the SEPSIS-2 definition excludes a number of patients with potentially deleterious infection because SIRS is absent in one of eight patients with infection and organ dysfunction.**

The old definitions

Defining criteria of ACCP/SCCM named conditions.

ACCP/SCCM named condition	Defining criteria
SIRS	Core body temperature >38°C or <36°C HR ≥90 bpm Respirations ≥20/min (or $PaCO_2$ <32 mmHg) WBC ≥12,000/μl or ≤4000/μl or >10% immature forms
Sepsis	At least two SIRS criteria caused by known or suspected infection
Severe sepsis	Sepsis with acute organ dysfunction (including hypoperfusion and hypotension) caused by sepsis
Septic shock	Sepsis with persistent or refractory hypotension or tissue hypoperfusion despite adequate fluid resuscitation
MODS	The presence of organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention

ACCP: American College of Chest Physicians; HR: Heart rate; MODS: Multiple organ dysfunction syndrome; $PaCO_2$: Partial pressure of carbon dioxide in the blood; SCCM: Society of Critical Care Medicine; SIRS: Systemic inflammatory response syndrome; WBC: White blood cell.

New definitions:

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection

NB:

- **The SIRS criteria have been removed**
- **It may be present in simple, non complicated infection, or in response to non infectious-triggers (i.e. trauma, pancreatitis, post-cardiac arrest synderome)**
- **Or may even be absent in critically ill patients with obvious evidence of a life-threatening infection.**

New definitions:

- **Organ dysfunction can be identified as an acute change in total SOFA score>2 points consequent to the infection**

- **A SOFA score>2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection.**

- **The baseline SOFA score can be assumed to be zero or in patients not known to have preexisting organ dysfunction**

New definitions

- **Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality**

Clinical criteria identifying such condition include the need for vasopressors to obtain a MAP≥ 65 mmHg and an increase in lactate concentration > 2 mmol/L, despite adequate fluid resuscitation.

Terms like severe sepsis/septicemia have been removed

New definitions (the screening tool)

- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA,
  - Respiratory rate ≥22/min
  - Altered mentation
  - Systolic blood pressure ≤ 100mmHg
    - **The presence of at least two of these criteria strongly predicts the likelihood of poor outcome in out-of-ICU patients with clinical suspicion of sepsis.**

- Sepsis : A life-threatening organ dysfunction caused by a dysregulated host response to infection.

- SOFA score ≥ 2 points = organ dysfunction

- SOFA score to evaluate sepsis in ICU settings
- qSOFA score to evaluate sepsis outside the ICU

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[25], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

© 2017 SCCM and ESICM

TABLE 6. SURVIVING SEPSIS CAMPAIGN BUNDLE 2016

To be completed within 3 hours

1. Measure lactate level.
2. Obtain blood cultures prior to administration of antibiotics.
3. Administer broad spectrum antibiotics.
4. Administer 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.

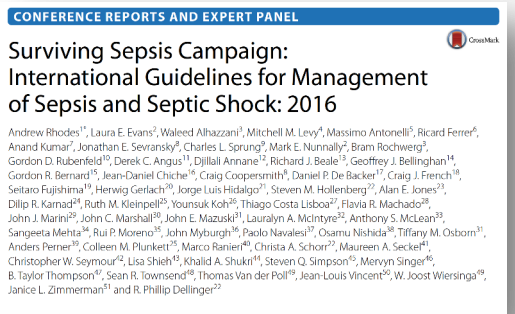
''Time of presentation'' is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

To be completed within 6 hours

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg.
6. In the event of persistent hypotension after initial fluid administration (MAP <65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.

D: ANTIMICROBIAL THERAPY (1)

- **1. We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within one hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).**

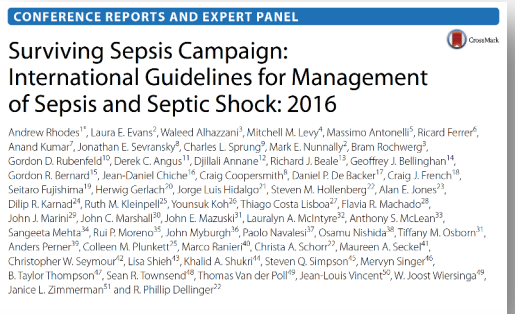

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[35], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[19], Jean-Louis Vincent[49], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

D: ANTIMICROBIAL THERAPY (2)

- **2. We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (strong recommendation, moderate quality of evidence).**
- **3. We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (BPS).**


CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[35], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[19], Jean-Louis Vincent[20], W. Joost Wiersinga[49], Janice L. Zimmerman[31] and R. Phillip Dellinger[22]

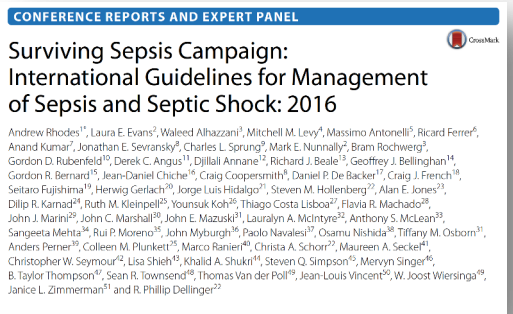
Several factors must be assessed and used in determining the appropriate antimicrobial regimen at eachmedical center and for each patient. These include:

a) **The anatomic site** of infection with respect to the typical pathogen profile and to the properties of individual antimicrobials to **penetrate that site**

b) **Prevalent pathogens** within the community, hospital, and even hospital ward

c) The **resistance** patterns of those prevalent pathogens

d) The presence of **specific immune defects** such as neutropenia, splenectomy, poorly controlled HIV infection and acquired or congenital defects of immunoglobulin, complement or leukocyte function or production

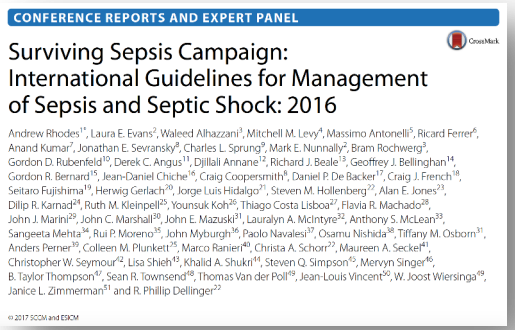

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[35], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[19], Jean-Louis Vincent[20], W. Joost Wiersinga[49], Janice L. Zimmerman[31] and R. Phillip Dellinger[22]

e) Age and patient comorbidities including chronic illness (e.g., diabetes) and chronic organ dysfunction (e.g., liver or renal failure), the presence of invasive devices (e.g., central venous lines or urinary catheter) that compromise the defense to infection.

f) Risk factors for infection with multidrug-resistant pathogens including prolonged hospital/chronic facility stay, recent antimicrobial use, prior hospitalization, and prior colonization or infection with multidrug- resistant organisms.


CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[25], Marco Ranieri[40], Christa A. Schorr[27], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

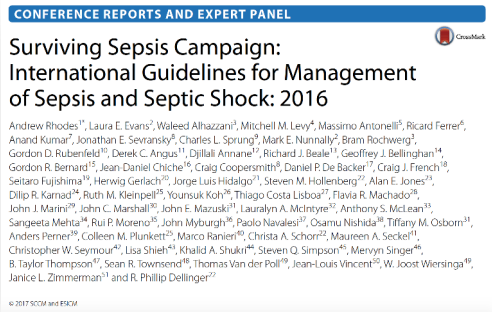
© 2017 SCCM and ESICM

g) Consider risk factors for: carbapenem resistant Gram negative rods (add a second agent….), MRSA, and legionella

l) Consider risk factors for Candida spp (echinocandins in critically ill pts): β-D-glucan?

m) Superior empiric coverage can be obtained using local and unit-specific antibiograms or an infectious diseases consultation. Where uncertainty regarding appropriate patient-specific antimicrobial therapy exists, infectious diseases consultation is warranted. Early involvement of infectious diseases specialists can improve outcome in some circumstances (e.g., *S aureus* bacteremia)

n) The decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and clinical information.


CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

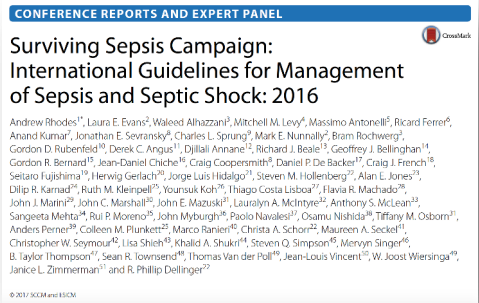
Andrew Rhodes[1], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[39], Anders Perner[39], Colleen M. Plunkett[25], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

© 2017 SCCM and ESICM

D: ANTIMICROBIAL THERAPY (3)

- **4. We recommend against sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury) (BPS).**
  - Although the prophylactic use of systemic antimicrobials for severe necrotizing pancreatitis has been recommended in the past, recent guidelines have favored avoidance of this approach
  - Current guidelines for burn management do not support sustained antimicrobial prophylaxis

- **5. We recommend that dosing strategies of antimicrobials be optimized based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock (BPS).**


CONFERENCE REPORTS AND EXPERT PANEL

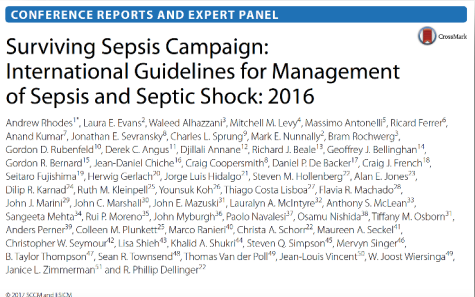
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[10], Bram Rochwerg[3], Gordon D. Rubenfeld[11], Derek C. Angus[12], Djillali Annane[13], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[39], Anders Perner[39], Colleen M. Plunkett[23], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

© 2017 SCCM and ESICM

D: ANTIMICROBIAL THERAPY (4)

6. We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock (weak recommendation, low quality of evidence).


CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[39], Anders Perner[39], Colleen M. Plunkett[22], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51], and R. Phillip Dellinger[22]

© 2017 SCCM and ESICM

Take home messages

- **Sepsis-3 is a helpful tool for identifying severe organ dysfunction and rapid progression to septic shock and ICU admission**

- **However, Sepsis-3 diagnostic criteria narrow the sepsis population at the expense of sensitivity (false negatives may have delayed diagnosis)**

- **Diagnostic management includes SOFA and qSOFA, but clinicians should be aware that both SOFA and qSOFA do not define sepsis, but instead might serve as indicators of an increased risk of death among patients with infection**