Journal Club
Surviving Sepsis Campaign Guideline 2016

2017/02/14

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救急集中治療科
有野　聡

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

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Crit Care Med 2017; 3:00–00

背景

- 2002年The Surviving Sepsis Campaign (SSC)

→29470人の観察研究では死亡率減

（odds ratio, 0.96; 95%%CI, 0.95-97; p < .001）

- The Surviving Sepsis Guidelinesは2004年に発表、2008年と2012年に改定

- 4版目を2017年１月のSCCMで発表

ガイドライン作成のプロセス

ガイドラインの範囲の制定
パネルメンバーの選定
古いPICOのreviewと新規PICOの作成
文献検索
systematic review
エビデンスの分析
recommendationの形成、grading
投票（80%の同意が必要）
再構築と再投票

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) systemの記載

	2012	2016
strength	1 2	Strong Weak
quality	A B C D	High Moderate Low Very Low
ungraded strong recommendation	ungraded strong recommendation	Best Practice Statement(BPS)

GRADEを決める5要因

- 研究の限界（limitations）
- 結果の非一貫性（inconsistency）

  結果に異質性があるか？
- エビデンスの非直接性（indirectness）

  外的妥当性はどうか？
- データの不精確さ（imprecision）

  データのばらつきは？信頼区間は？
- 出版バイアス（publication bias）

Recommendationの強さの意義

	strong	weak
患者にとって	ほとんどの人は推奨されたコースを希望するだろう。一部は異なる。	多数派は推奨されたコースを希望するだろうが、異なる人も多い。
臨床医にとって	ほとんどの患者が推奨された診療を受けるべき。	異なる患者には異なる選択が適切になる可能性が高い。治療は個々の患者の環境に合わせて調整されるべき。
医療政策決定者にとって	ほとんどの状況で推奨をそのまま政策に適応でき、標準の尺度になる。	政策を作成するには関係者を含んでかなりの議論が必要。

Recommendations

- 93のPICO questionsに対して声明
  - 32のstrong recommendations
  - 39のweak recommendations
  - 18のBest Practice Statements
  - 4のPICOにはno recommendation

Recommendations

A. INITIAL RESUSCITATION
B. SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT
C. DIAGNOSIS
D. ANTIMICROBIAL THERAPY
E. SOURCE CONTROL
F. FLUID THERAPY
G. VASOACTIVE MEDICATIONS
H. CORTICOSTEROIDS
I. BLOOD PRODUCTS
J. IMMUNOGLOBULINS
K. BLOOD PURIFICATION
L. ANTICOAGULANTS
M. MECHANICAL VENTILATION
N. SEDATION AND ANALGESIA
O. GLUCOSE CONTROL
P. RENAL REPLACEMENT THERAPY
Q. BICARBONATE THERAPY
R. VENOUS THROMBOEMBOLISM PROPHYLAXIS
S. STRESS ULCER PROPHYLAXIS
T. NUTRITION
U. SETTING GOALS OF CARE

21の分野

2012の推奨

A. INITIAL RESUSCITATION

1. Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hours of resuscitation:
   a. Central venous pressure 8–12 mm Hg
   b. Mean arterial pressure ≥ 65 mm Hg
   c. Urine output ≥ 0.5 mL/kg/hr
   d. Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels, targeting resuscitation to normalize lactate (grade 2C).

ココがnew point

- EGDTの記載が消失
- 最低輸液量の明記（3時間以内に30mL/kgの晶質液）
- MAP65mmHgの目標はそのまま

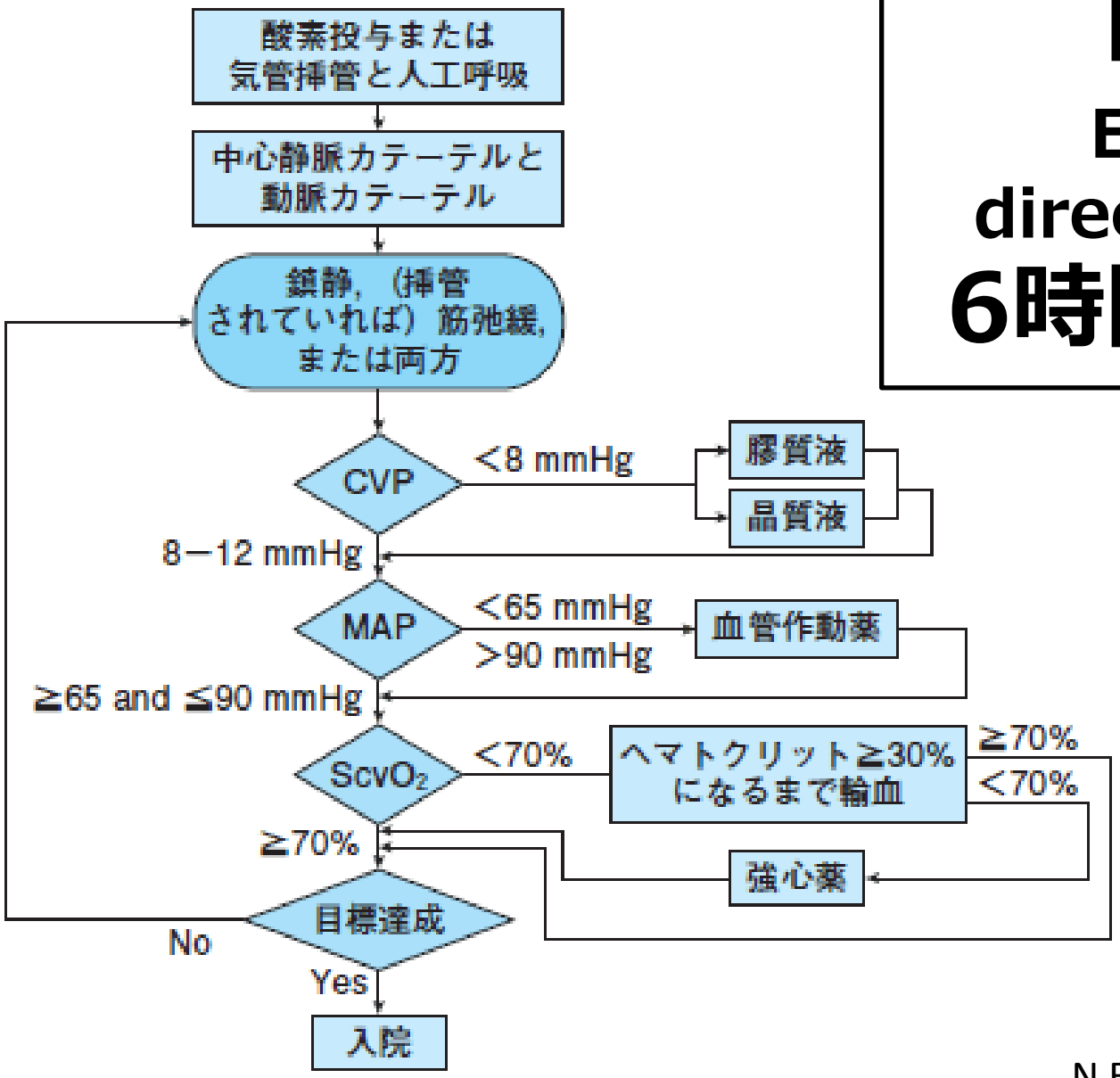
2016の推奨

A. INITIAL RESUSCITATION

1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately (BPS).
2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence).
3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).

Remarks: Reassessment should include a thorough clinical examination and evaluation of available physiologic variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others, as available) as well as other noninvasive or invasive monitoring, as available.

4. We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis (BPS).
5. We suggest that dynamic over static variables be used to predict fluid responsiveness, where available (weak recommendation, low quality of evidence).
6. We recommend an initial target mean arterial pressure of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).
7. We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).



EGDT

Early goal directed therapy

6時間以内に達成

院内死亡率

EGDT

30.5%

Usual Care

46.5%

N Engl J Med 2001;345:1368-77

https://www.igaku-shoin.co.jp/paperDetail.do?id=PA03102_02#bun2

CVPは輸液を入れるかどうかの指標になる？

Does the Central Venous Pressure Predict Fluid Responsiveness? An Updated Meta-Analysis and a Plea for Some Common Sense*

Paul E. Marik, MD, FCCM[1]; Rodrigo Cavallazzi, MD[2]

CVPの輸液反応性に関する43研究をまとめたもの

ROC曲線下面積 0.56 (95%CI 0.52-0.60)

筆者らのコメント

CVPを使うことは
コインをはじいて決めるのと同じ

輸液を入れるかどうかの指標
まとめ

- 静的指標
  CVP、PAWP、左室拡張末期面積（心エコー）
- 動的指標
  SVV、PPV、SPV
  IVC径の呼吸性変動
  LVOT-VTIの呼吸性変動
- 機能試験
  足上げ試験（PLR）
  輸液負荷試験

平均血圧の目標は65mmHg？

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

High versus Low Blood-Pressure Target in Patients with Septic Shock

MAP 65-70 **MAP 80-85**

- 死亡率は両群間で変わりなし
- 高めの目標群で、心房細動が多い
- 高血圧の既往がある患者では、高めの目標群で透析の必要性が減少

MAPの目標値は65mmHgとしてよいが、患者ごとに目標を設定してもいいかも

$ScvO_2$ vs Lactate

JAMA

Online article and related content current as of October 24, 2010.

Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial

Alan E. Jones; Nathan I. Shapiro; Stephen Trzeciak; et al.

JAMA. 2010;303(8):739-746 (doi:10.1001/jama.2010.158)

院内死亡率

$ScvO_2$	Lactate
22.7%	16.7%

$ScvO_2$とLactateのどちらを指標にしても予後は変わらない

敗血症における輸血の閾値

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 9, 2014 VOL. 371 NO. 15

Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

90日死亡率

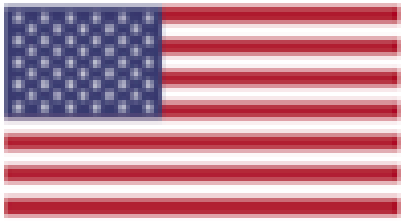
Hb 9g/dL	Hb 7g/dL
45%	43%

敗血症性ショックにおける輸血閾値は Hb 7g/dLで良さそう

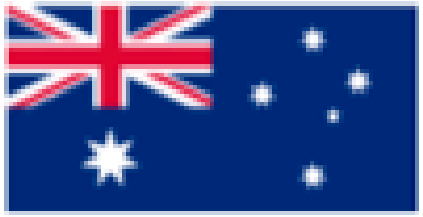
N Engl J Med 2014;371:1381-91.

EGDTは有効なのか？

ProCESS



ARISE

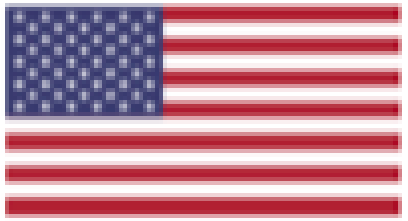


ProMISe

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

ProCESS



A Randomized Trial of Protocol-Based Care for Early Septic Shock

60日死亡率

EGDT	Usual Care
21.0%	18.9%

- 死亡率に有意差なし
- 昇圧薬使用、人工呼吸器使用に有意差なし
- ICU滞在期間、入院期間、重大な合併症イベントに有意差なし

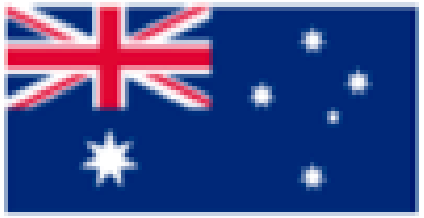
N Engl J Med 2014;370:1683-93.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

ARISE



90日死亡率

EGDT	Usual Care
18.6%	18.8%

- 死亡率に有意差なし
- EGDT群で最初の6時間に投与された輸液量が多い
- EGDT群で昇圧薬使用、DOB使用、輸血が多い

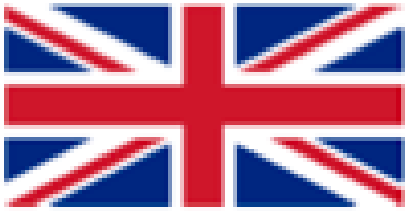
N Engl J Med 2014;371:1496-506.

The NEW ENGLAND JOURNAL of MEDICINE

ProMISe

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock



90日死亡率

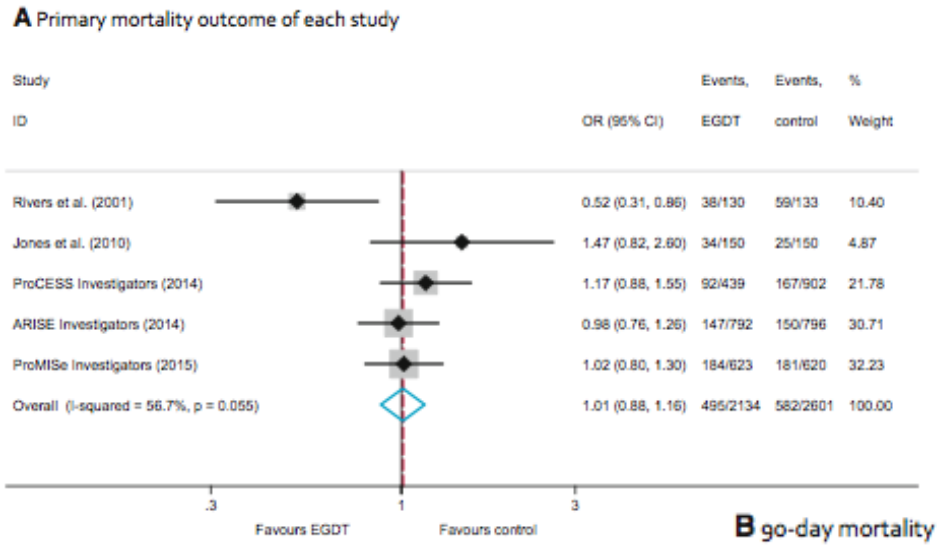
EGDT	Usual Care
29.5%	29.2%

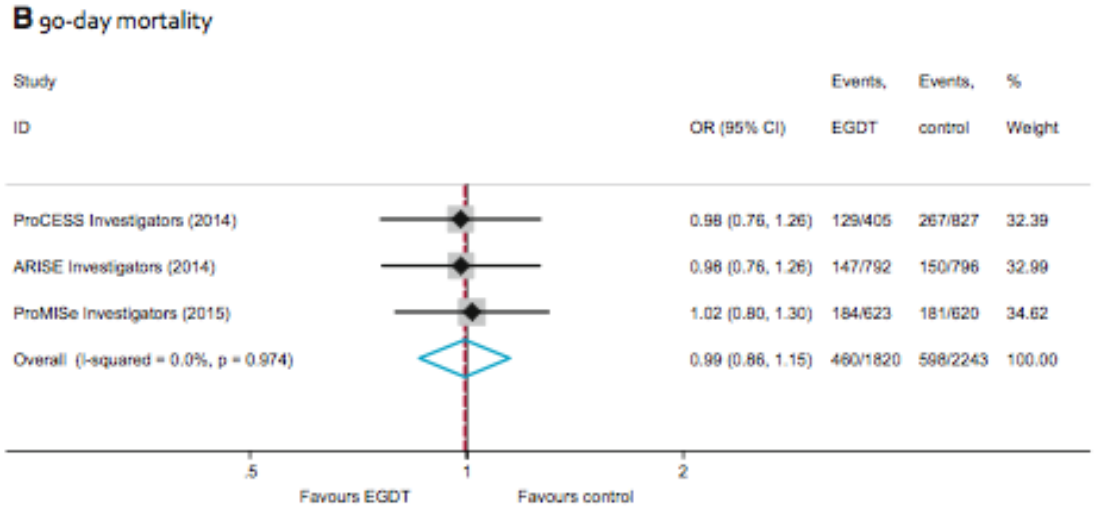
- 死亡率に有意差なし
- EGDT群で輸液量、昇圧薬使用、DOB使用、輸血が多い
- EGDT群でICU滞在期間が長い

N Engl J Med 2014;371:1496-506.

A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

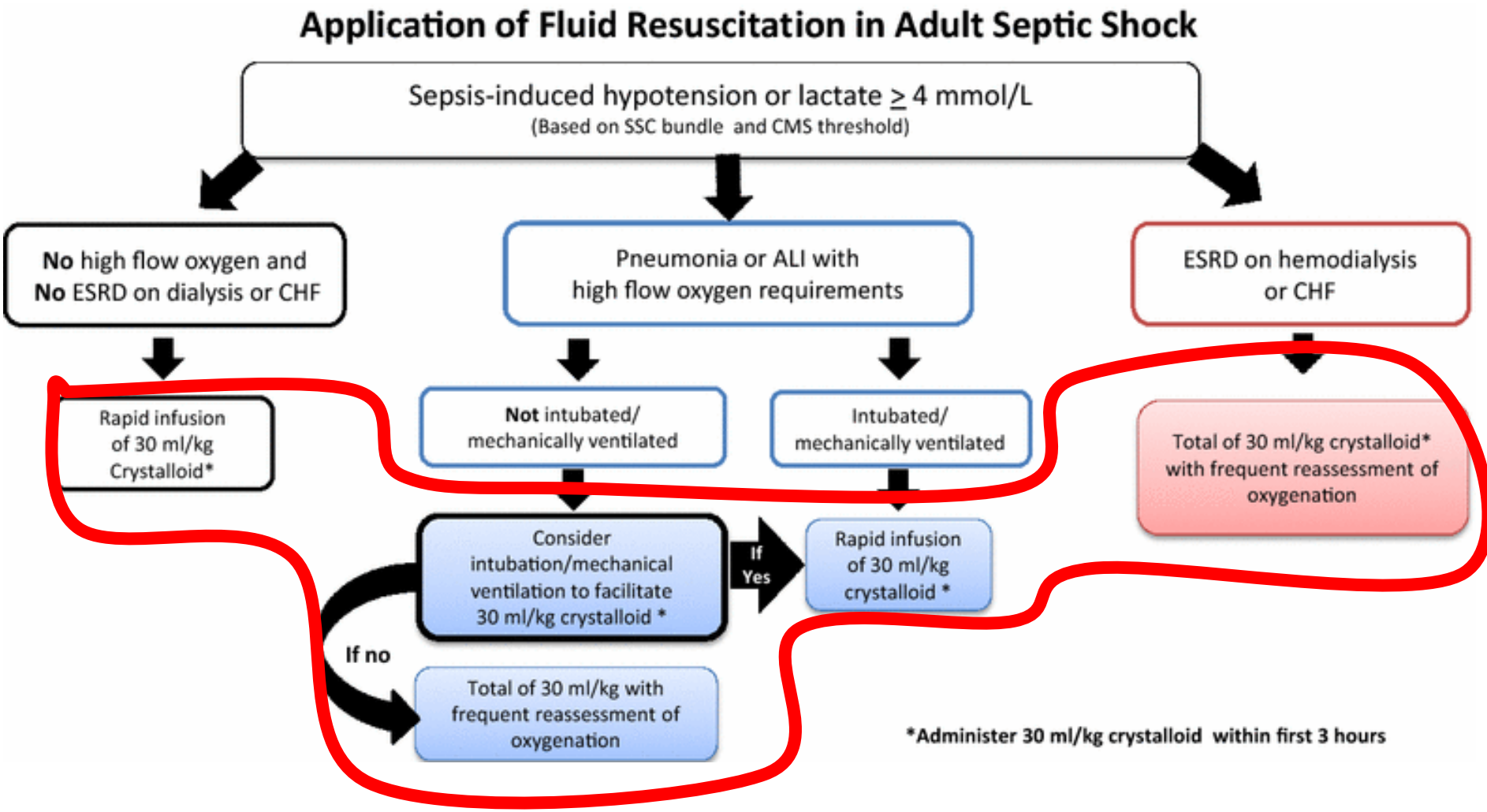
Intensive Care Med 2015 41:1549–1560





90日死亡率に有意差なし

A users' guide to the 2016 Surviving Sepsis Guidelines. Intensive Care Med. 2017 Jan 18.



リスクによって酸素化に注意・挿管を考慮するが、
30ml/kgの晶質液を輸液することが重要

Fig. 2 This figure explores the nuancing of initial administration of 30 ml/kg crystalloid for sepsis induced hypoperfusion based on patient characteristics. It also draws attention to reassessment tools following the initial fluid dose as an influence on further fluid administration or inotropic therapy

A users' guide to the 2016 Surviving Sepsis Guidelines. Intensive Care Med. 2017 Jan 18.

晶質液を30ml/kg投与した後は…

1. 組織還流の維持と間質浮腫が最小限になる事に注意しながらfluid resuscitationと昇圧剤を継続

2. 追加の蘇生（追加輸液や循環作動薬など）を下記組み合わせで選択
   - 血圧、心拍数の反応
   - 尿量
   - 心胸郭超音波
   - CVP、ScvO2
   - pulse pressure variation
   - 乳酸クリアランス
   - ボーラス注射や下肢挙上への反応など、循環動態の動的評価

3. 血管内volumeの維持に多量の晶質液が必要であればアルブミンの投与を考慮

SSCGバンドル2015は改変なし？

3時間以内に達成すべき項目

1）乳酸値を測定する

2）抗生剤投与前に血液培養を採取する

3）広域抗生剤を投与する

4）低血圧もしくは乳酸値≧4mmol/Lに対して30mL/kgの晶質液を投与する

6時間以内に達成すべき項目

5）（初期輸液蘇生に反応しない低血圧に対して）平均血圧（MAP）≧65mmHgを維持するように昇圧薬を投与する

6）輸液蘇生にもかかわらず低血圧が遷延する（敗血症性ショック）もしくは治療初期の乳酸値が4mmol/L（36mg/dL）以上であったとき：

・中心静脈圧（CVP）*を測定する

・上大静脈血酸素飽和度（Scv_{O_2}）*を測定する

7）治療初期の乳酸値が上昇していた場合は乳酸値を再測定する*

*ガイドラインに示される数値目標は、CVP≧8mmHg、Scv_{O_2}≧70%、乳酸値の正常化

心エコー
PLRテスト

図1. Surviving Sepsis Campaignのケアバンドル

Surviving Sepsis Campaign

Updated Bundles in Response to New Evidence

B. SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C).
2. Hospital-based performance improvement efforts in severe sepsis (UG).

B. SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

1. We recommend that hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients (BPS).

C. DIAGNOSIS

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 min) in the start of antimicrobials (grade 1C). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (< 48 hrs) inserted (grade 1C).
2. Use of the 1,3-ß-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available, and invasive candidiasis in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection (UG).

C. DIAGNOSIS

1. We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock if doing so results in no substantial delay in the start of antimicrobials (BPS).

Remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).

ココがnew point

- シンプル化
- 目立った変化なし

D. ANTIMICROBIAL THERAPY

1. Administration of effective IV antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.
2. Initial empiric antiinfective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).
3. Antimicrobial regimen should be reassessed daily for potential de-escalation (grade 1B).
4. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).
5. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* species (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended-spectrum ß-lactam and either an aminoglycoside or a fluoroquinolone for *Pseudomonas aeruginosa* bacteremia (grade 2B). A combination of ß-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).
6. Empiric combination therapy should not be administered for more than 3 to 5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).
7. Duration of therapy typically 7 to 10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus*, some fungal and viral infections, or immunologic deficiencies, including neutropenia (grade 2C).

D. ANTIMICROBIAL THERAPY

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).
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 antimicrobial therapy is narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (BPS).
4. We recommend against sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury) (BPS).
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).
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). Remarks: Readers should review Table 6 for definitions of empiric, targeted/definitive, broad-spectrum, combination, and multidrug therapy before reading this section.
7. We suggest that combination therapy not be routinely used for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock (weak recommendation, low quality of evidence). Remarks: This does not preclude the use of multidrug therapy to broaden antimicrobial activity.
8. We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteremia (strong recommendation, moderate quality of evidence). Remarks: This does not preclude the use of multidrug therapy to broaden antimicrobial activity.

8. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).
9. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

9. If combination therapy is used for septic shock, we recommend de-escalation with discontinuation of combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution. This applies to both targeted (for culture-positive infections) and empiric (for culture-negative infections) combination therapy (BPS).
10. We suggest that an antimicrobial treatment duration of 7 to 10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence).
11. We suggest that longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus*, some fungal and viral infections, or immunologic deficiencies, including neutropenia (Weak recommendation, low quality of evidence).
12. We suggest that shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis (weak recommendation, low quality of evidence).
13. We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock (BPS).
14. We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence).
15. We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence).

ココがnew point

- 抗菌薬のルーチンな併用はダメ
- プロカルシトニンの有用性に言及（weak recommendation）

E. SOURCE CONTROL

1. A specific anatomic diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hours after the diagnosis is made, if feasible (grade 1C).
2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).
3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess) (UG).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

E. SOURCE CONTROL

1. We recommend that a specific anatomic diagnosis of infection requiring emergent source control should be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention should be implemented as soon as medically and logistically practical after the diagnosis is made (BPS).
2. We recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established (BPS).

ココがnew point

- シンプル化
- 目立った変化なし

F. FLUID THERAPY

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables (UG).

F. FLUID THERAPY

1. We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve (BPS).
2. We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).
3. We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).
4. We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock, when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).
5. We recommend against using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).
6. We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

ココがnew point

- HESはダメ

G. VASOACTIVE MEDICATIONS

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first-choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin, 0.03 units/minute, can be added to norepinephrine with intent of either raising MAP or decreasing norepinephrine dosage (UG).
5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension, and vasopressin doses higher than 0.03–0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).
10. A trial of dobutamine infusion up to 20 µg/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).

G. VASOACTIVE MEDICATIONS

1. We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).
2. We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising mean arterial pressure to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.
3. We suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (weak recommendation, low quality of evidence).
4. We recommend against using low-dose dopamine for renal protection (strong recommendation, high quality of evidence).
5. We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).

Remarks: If initiated, dosing should be titrated to an end point reflecting perfusion, and the agent reduced or discontinued in the face of worsening hypotension or arrhythmias.

6. We suggest that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (weak recommendation, very low quality of evidence).

11. Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

ココがnew point

- バソプレシンの重要性強調
- A-lineの重要性強調

A users' guide to the 2016 Surviving Sepsis Guidelines. Intensive Care Med. 2017 Jan 18.

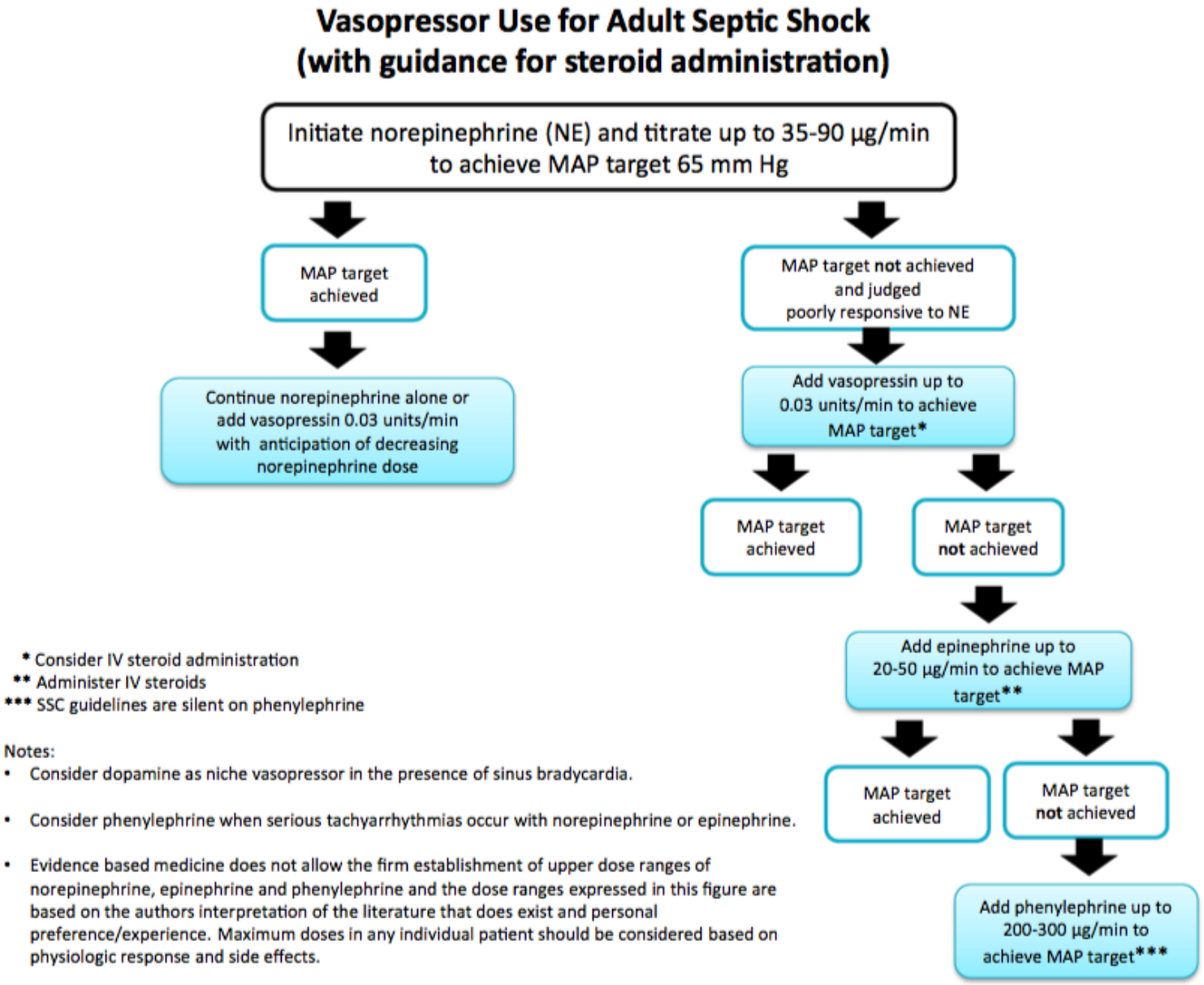
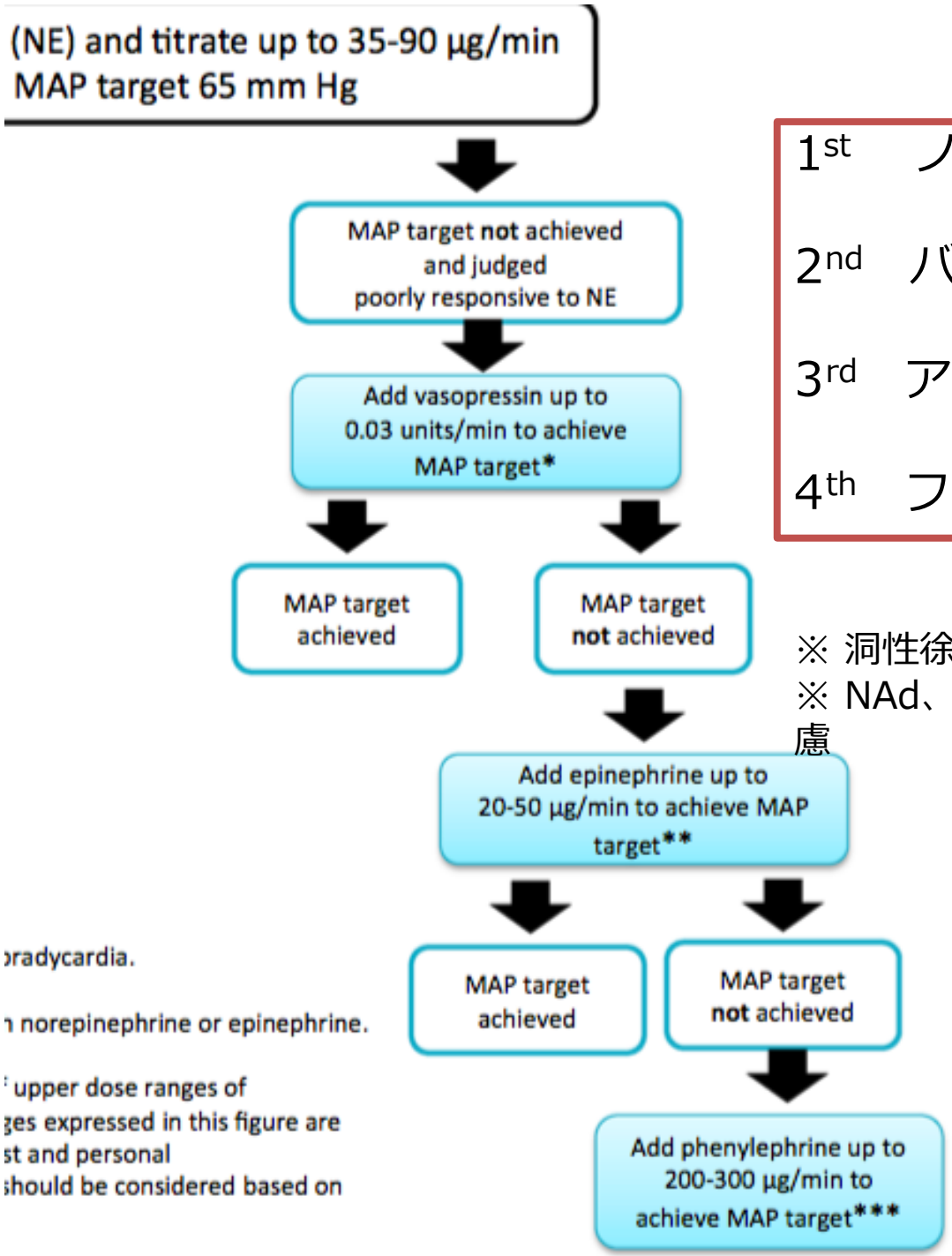


Fig. 3 This figure demonstrates how the guideline recommendations on vasopressor and steroid use can be molded into a flow diagram approach to the management of septic shock



1st　ノルアドレナリン 35-90 µg/min
↓□ステロイドIV考慮
2nd　バソプレシン 0.03 U/min
↓□ステロイドIV導入
3rd　アドレナリン 25−50 µg/min
↓□
4th　フェニレフリン 200−300 µg/min

※ 洞性徐脈➡□DOAを考慮
※ NAd、Adで頻脈性不整脈➡□フェニレフリン考慮

H. CORTICOSTEROIDS

1. Not using IV hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest IV hydrocortisone alone at a dose of 200 mg/day (grade 2C).
2. Not using the adrenocorticotropic hormone stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).
3. In treated patients, hydrocortisone tapered when vasopressors are no longer required (grade 2D).
4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).
5. When hydrocortisone is given, use continuous flow (grade 2D).

H. CORTICOSTEROIDS

1. We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

ココがnew point

- 持続注射の記載消失

I. BLOOD PRODUCTS

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic heart disease, we recommend that RBC transfusion occur only when hemoglobin concentration decreases to < 7.0 g/dL to target a hemoglobin concentration of 7.0–9.0 g/dL in adults (grade 1B).
2. Not using erythropoietin as a specific treatment of anemia associated with severe sepsis (grade 1B).
3. Fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D).
4. Not using antithrombin for the treatment of severe sepsis and septic shock (grade 1B).
5. In patients with severe sepsis, administer platelets prophylactically when counts are < 10,000/mm^3 (10×10^9/L) in the absence of apparent bleeding. We suggest prophylactic platelet transfusion when counts are < 20,000/mm^3 (20×10^9/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥ 50,000/mm^3 [50×10^9/L]) are advised for active bleeding, surgery, or invasive procedures (grade 2D).

I. BLOOD PRODUCTS

1. We recommend that RBC transfusion occur only when hemoglobin concentration decreases to < 7.0 g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage (trong recommendation, high quality of evidence).
2. We recommend against the use of erythropoietin for treatment of anemia associated with sepsis (strong recommendation, moderate quality of evidence).
3. We suggest against the use of fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedures (weak recommendation, very low quality of evidence).
4. We suggest prophylactic platelet transfusion when counts are < 10,000/mm^3 (10×10^9/L) in the absence of apparent bleeding and when counts are < 20,000/mm^3 (20×10^9/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥ 50,000/mm^3 [50×10^9/L]) are advised for active bleeding, surgery, or invasive procedures (weak recommendation, very low quality of evidence).

ココがnew point

- 目立った変化なし

J. IMMUNOGLOBULINS	**J. IMMUNOGLOBULINS**
1. Not using IV immunoglobulins in adult patients with severe sepsis or septic shock (grade 2B).	1. We suggest against the use of IV immunoglobulins in patients with sepsis or septic shock (weak recommendation, low quality of evidence).
K. BLOOD PURIFICATION	**K. BLOOD PURIFICATION**
Not applicable.	1. We make no recommendation regarding the use of blood purification techniques.
L. ANTICOAGULANTS	**L. ANTICOAGULANTS**
Not applicable.	1. We recommend against the use of antithrombin for the treatment of sepsis and septic shock (strong recommendation, moderate quality of evidence). 2. We make no recommendation regarding the use of thrombomodulin or heparin for the treatment of sepsis or septic shock.

ココがnew point

- 免疫グロブリン投与は変わらず否定的
- 血液浄化に現時点で推奨なし
- アンチトロンビンはダメ
- トロンボモジュリン、ヘパリンの推奨なし

M. MECHANICAL VENTILATION

1. Target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced acute respiratory distress syndrome (ARDS) (grade 1A vs. 12 mL/kg).
2. Plateau pressures be measured in patients with ARDS and initial upper-limit goal for plateau pressures in a passively inflated lung be ≤ 30 cm H_2O (grade 1B).
3. Positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end-expiration (atelectotrauma) (grade 1B).
4. Strategies based on higher rather than lower levels of PEEP be used for patients with sepsis-induced moderate or severe ARDS (grade 2C).
5. Recruitment maneuvers be used in sepsis patients with severe refractory hypoxemia (grade 2C).
6. Prone positioning be used in sepsis-induced ARDS patients with a Pao_2/Fio_2 ratio ≤ 100 mm Hg in facilities that have experience with such practices (grade 2B).
7. Mechanically ventilated sepsis patients be maintained with the head of the bed elevated to 30–45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (grade 1B).
8. Noninvasive mask ventilation (NIV) be used in that minority of sepsis-induced ARDS patients in whom the benefits of NIV have been carefully considered and are thought to outweigh the risks (grade 2B).
9. A weaning protocol be in place, and that mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate their ability to discontinue mechanical ventilation when they satisfy the following criteria: a) arousable, b) hemodynamically stable (without vasopressor agents), c) no new potentially serious conditions, d) low ventilatory and end-expiratory pressure requirements, and e) low Fio_2 requirements that can be met safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, consideration should be given for extubation (grade 1A).
10. Against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS (grade 1A).
11. A conservative rather than liberal fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (grade 1C).
12. In the absence of specific indications such as bronchospasm, not using ß-2 agonists for treatment of sepsis-induced ARDS (grade 1B).

M. MECHANICAL VENTILATION

1. We recommend using a target tidal volume of 6 mL/kg predicted body weight compared with 12 mL/kg in adult patients with sepsis-induced acute respiratory distress syndrome (ARDS) (strong recommendation, high quality of evidence).
2. We recommend using an upper limit goal for plateau pressures of 30 cm H_2O over higher plateau pressures in adult patients with sepsis-induced severe ARDS (strong recommendation, moderate quality of evidence).
3. We suggest using higher positive end-expiratory pressure (PEEP) over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS (weak recommendation, moderate quality of evidence).
4. We suggest using recruitment maneuvers in adult patients with sepsis-induced severe ARDS (weak recommendation, moderate quality of evidence).
5. We recommend using prone over supine position in adult patients with sepsis-induced ARDS and a Pao_2/Fio_2 ratio < 150 (strong recommendation, moderate quality of evidence).
6. We recommend against using high-frequency oscillatory ventilation in adult patients with sepsis-induced ARDS (strong recommendation, moderate quality of evidence).
7. We make no recommendation regarding the use of noninvasive ventilation for patients with sepsis-induced ARDS.
8. We suggest using neuromuscular blocking agents for ≤ 48 hours in adult patients with sepsis-induced ARDS and a Pao_2/Fio_2 ratio < 150 mm Hg (weak recommendation, moderate quality of evidence).
9. We recommend a conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (strong recommendation, moderate quality of evidence).
10. We recommend against the use of ß-2 agonists for the treatment of patients with sepsis-induced ARDS without bronchospasm (strong recommendation, moderate quality of evidence).
11. We recommend against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS (strong recommendation, high quality of evidence).
12. We suggest using lower tidal volumes over higher tidal volumes in adult patients with sepsis-induced respiratory failure without ARDS (weak recommendation, low quality of evidence).

鎮静、鎮痛の項から移動

13. We recommend that mechanically ventilated sepsis patients be maintained with the head of the bed elevated between 30 and 45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (strong recommendation, low quality of evidence).
14. We recommend using spontaneous breathing trials in mechanically ventilated patients with sepsis who are ready for weaning (strong recommendation, high quality of evidence).
15. We recommend using a weaning protocol in mechanically ventilated patients with sepsis-induced respiratory failure who can tolerate weaning (strong recommendation, moderate quality of evidence).

ココがnew point

- P/F<150mmHgに対する腹臥位（strong recommendation）
- P/F<150mmHgに対する筋弛緩（weak recommendation）
- HFOVには否定的
- head up、SBT、weaning protocolの推奨

N. SEDATION AND ANALGESIA

1. Continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration end points (grade 1B).
2. Neuromuscular blocking agents (NMBAs) be avoided if possible in septic patients without ARDS due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of the depth of blockade should be used (grade 1C).
3. A short course of NMBA of not greater than 48 hours for patients with early sepsis-induced ARDS and a Pao_2/Fio_2 ratio < 150 mm Hg (grade 2C).

Mの項に移動

N. SEDATION AND ANALGESIA

1. We recommend that continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration endpoints (BPS).

ココがnew point

- 目立った変化なし

O. GLUCOSE CONTROL

1. A protocolized approach to blood glucose management in ICU patients with severe sepsis commencing insulin dosing when consecutive blood glucose levels are > 180 mg/dL. This protocolized approach should target an upper blood glucose level ≤ 180 mg/dL rather than an upper target blood glucose level ≤ 110 mg/dL (grade 1A).
2. Blood glucose values be monitored every 1 to 2 hours until glucose values and insulin infusion rates are stable and then every 4 hours thereafter (grade 1C).
3. Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (UG).

O. GLUCOSE CONTROL

1. We recommend a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when two consecutive blood glucose levels are > 180 mg/dL. This approach should target an upper blood glucose level ≤ 180 mg/dL rather than an upper target blood glucose level ≤ 110 mg/dL (strong recommendation, high quality of evidence).
2. We recommend that blood glucose values be monitored every 1 to 2 hours until glucose values and insulin infusion rates are stable, then every 4 hours thereafter in patients receiving insulin infusions (BPS).
3. We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (BPS).
4. We suggest the use of arterial blood rather than capillary blood for point-of-care testing using glucose meters if patients have arterial catheters (weak recommendation, low quality of evidence).

ココがnew point

- 目立った変化なし
- A-lineがあれば動脈血で血糖測定

P. RENAL REPLACEMENT THERAPY

1. Continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure (grade 2B).
2. Use continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients (grade 2D).

P. RENAL REPLACEMENT THERAPY

1. We suggest that either continuous or intermittent renal replacement therapy (RRT) be used in patients with sepsis and acute kidney injury (weak recommendation, moderate quality of evidence).
2. We suggest using continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients (weak recommendation, very low quality of evidence).
3. We suggest against the use of RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis (weak recommendation, low quality of evidence).

ココがnew point

- Creの上昇や乏尿という理由だけで透析をすることには否定的

Q. BICARBONATE THERAPY

1. Not using sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15 (grade 2B).

R. VENOUS THROMBOEMBOLISM (VTE) PROPHYLAXIS

1. Patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE) (grade 1B). This should be accomplished with daily subcutaneous low-molecular-weight heparin (LMWH) (grade 1B versus twice daily unfractionated heparin [UFH], grade 2C versus three times daily UFH). If creatinine clearance is < 30 mL/min, use dalteparin (grade 1A) or another form of LMWH that has a low degree of renal metabolism (grade 2C) or UFH (grade 1A).
2. Patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible (grade 2C).
3. Septic patients who have a contraindication for heparin use (e.g., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage) not receive pharmacoprophylaxis (grade 1B), but receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices (grade 2C), unless contraindicated. When the risk decreases, start pharmacoprophylaxis (grade 2C).

Q. BICARBONATE THERAPY

1. We suggest against the use of sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15 (weak recommendation, moderate quality of evidence).

R. VENOUS THROMBOEMBOLISM PROPHYLAXIS

1. We recommend pharmacologic prophylaxis (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) against venous thromboembolism (VTE) in the absence of contraindications to the use of these agents (strong recommendation, moderate quality of evidence).
2. We recommend LMWH rather than UFH for VTE prophylaxis in the absence of contraindications to the use of LMWH (strong recommendation, moderate quality of evidence).
3. We suggest combination pharmacologic VTE prophylaxis and mechanical prophylaxis, whenever possible (weak recommendation, low quality of evidence).
4. We suggest mechanical VTE prophylaxis when pharmacologic VTE is contraindicated (weak recommendation, low quality of evidence).

ココがnew point

- 目立った変化なし

S. STRESS ULCER PROPHYLAXIS	S. STRESS ULCER PROPHYLAXIS
1. Stress ulcer prophylaxis using histamine-2 blocker or proton pump inhibitor be given to patients with severe sepsis or septic shock who have bleeding risk factors (grade 1B).	1. We recommend that stress ulcer prophylaxis be given to patients with sepsis or septic shock who have risk factors for gastrointestinal (GI) bleeding (strong recommendation, low quality of evidence).
2. When stress ulcer prophylaxis is used, proton pump inhibitors rather than histamine-2 receptor antagonists (grade 2D).	2. We suggest using either proton pump inhibitors or histamine-2 receptor antagonists when stress ulcer prophylaxis is indicated (weak recommendation, low quality of evidence).
3. Patients without risk factors do not receive prophylaxis (grade 2B).	3. We recommend against stress ulcer prophylaxis in patients without risk factors for GI bleeding (BPS).

ココがnew point

・PPI>H2blockerではなく、
PPI=H2 blockerの記載に変更

T. NUTRITION

1. Administer oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only IV glucose within the first 48 hours after a diagnosis of severe sepsis or septic shock (grade 2C).
2. Avoid mandatory full caloric feeding in the first week but rather suggest low-dose feeding (e.g., up to 500 calories per day), advancing only as tolerated (grade 2B).
3. Use IV glucose and enteral nutrition rather than total parenteral nutrition alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis or septic shock (grade 2B).
4. Use nutrition with no specific immunomodulating supplementation rather than nutrition providing specific immunomodulating supplementation in patients with severe sepsis (grade 2C).
5. Not using IV selenium for the treatment of severe sepsis (grade 2C).

T. NUTRITION

1. We recommend against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally (strong recommendation, moderate quality of evidence).
2. We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not feasible (strong recommendation, moderate quality of evidence).
3. We suggest the early initiation of enteral feeding rather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally (weak recommendation, low quality of evidence).
4. We suggest either early trophic/hypocaloric or early full enteral feeding in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance (weak recommendation, moderate quality of evidence).
5. We recommend against the use of omega-3 fatty acids as an immune supplement in critically ill patients with sepsis or septic shock (strong recommendation, low quality of evidence).
6. We suggest against routinely monitoring gastric residual volumes in critically ill patients with sepsis or septic shock (weak recommendation, low quality of evidence). However, we suggest measurement of gastric residuals in patients with feeding intolerance or who are considered to be at high risk of aspiration (weak recommendation, very low quality of evidence).

Remarks: This recommendation refers to nonsurgical critically ill patients with sepsis or septic shock.

7. We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance (weak recommendation, low quality of evidence).

8. We suggest placement of post-pyloric feeding tubes in critically ill patients with sepsis or septic shock with feeding intolerance or who are considered to be at high risk of aspiration (weak recommendation, low quality of evidence).
9. We recommend against the use of IV selenium to treat sepsis and septic shock (strong recommendation, moderate quality of evidence).
10. We suggest against the use of arginine to treat sepsis and septic shock (weak recommendation, low quality of evidence).
11. We recommend against the use of glutamine to treat sepsis and septic shock (strong recommendation, moderate quality of evidence).
12. We make no recommendation about the use of carnitine for sepsis and septic shock.

ココがnew point

- 静脈栄養は7日間は避ける
- 経腸栄養は少量からでもfullからでもOKで早期に開始
- 胃残の測定は経腸栄養が進まない場合や誤嚥のhigh riskの人に選択的に
- 推奨：経腸栄養が進まないなら蠕動促進薬、十二指腸栄養
- 推奨しない：オメガ3脂肪酸、静注セレン、アルギニン、グルタミン、（カルニチン）

U. SETTING GOALS OF CARE	U. SETTING GOALS OF CARE
1. Discuss goals of care and prognosis with patients and families (grade 1B).	1. We recommend that goals of care and prognosis be discussed with patients and families (BPS).
2. Incorporate goals of care into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (grade 1B).	2. We recommend that goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (strong recommendation, moderate quality of evidence).
3. Address goals of care as early as feasible, but no later than within 72 hours of ICU admission (grade 2C).	3. We suggest that goals of care be addressed as early as feasible, but no later than within 72 hours of ICU admission (weak recommendation, low quality of evidence).

ココがnew point

- 目立った変化なし

SSCG2016最重要point

- EGDTが推奨からの削除
- 30ml/kgの晶質液で初期蘇生
- 初期蘇生後は各種パラメーターを用いて、必要と判断された場合に輸液を入れる
- 昇圧剤はNAd→バソプレシン→Ad→フェニレフリン
- バソプレシン開始でステロイド投与を考慮

- プロカルシトニンを抗菌薬中止基準として弱く推奨
- 腹臥位療法がP/F 150以下のARDSに対して強く推奨
- PPI=H2 blockerとなった