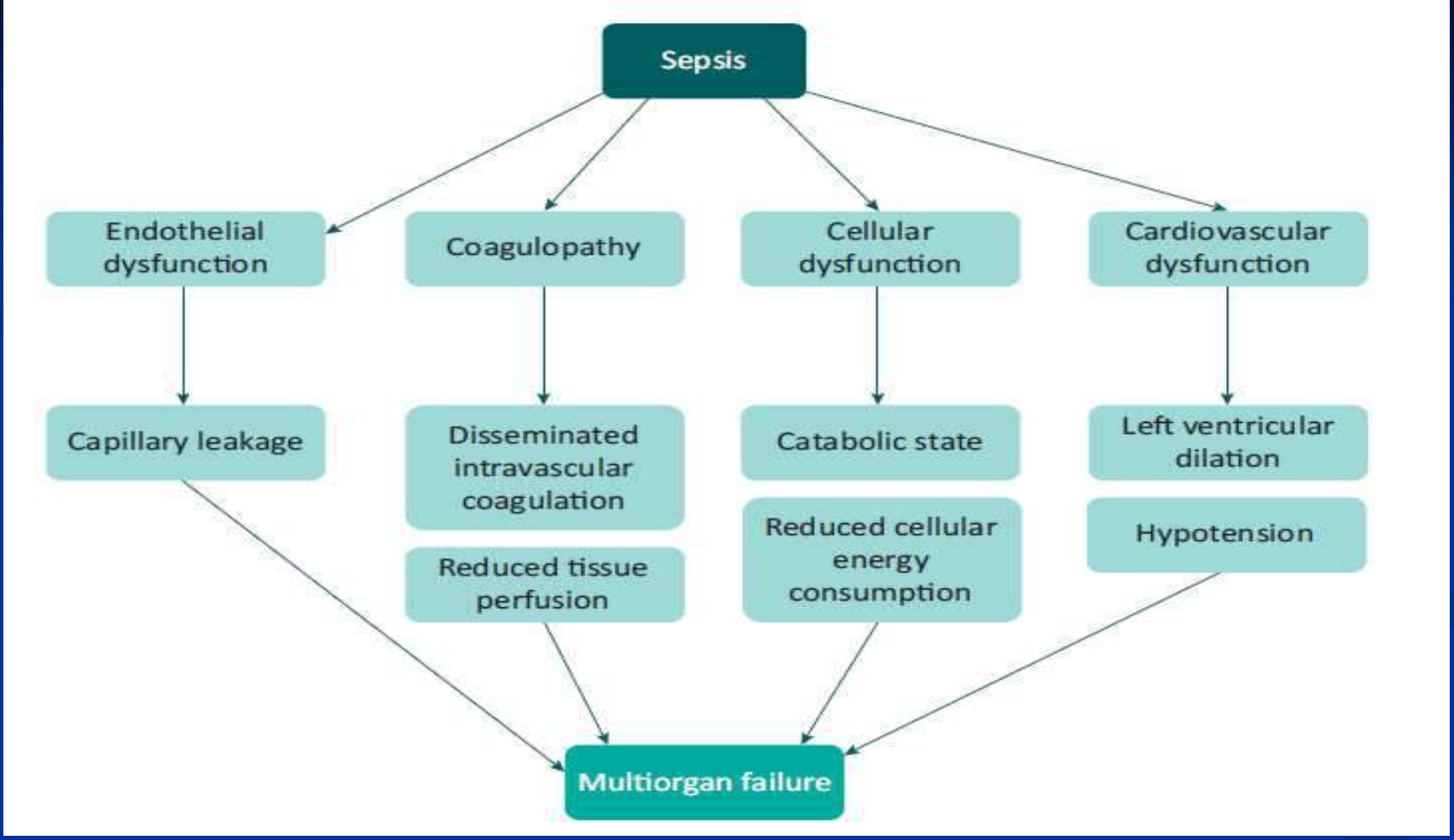


- The key pathophysiological changes of sepsis and how these combine to produce multiorgan failure.

Tom Evans. Clinical Medicine 2018 Vol l8, No 2 : 61:4 164–69

- Source of infection of septic patients admitted to ICUs worldwide:
  - the lungs (64%),
  - abdomen (20%),
  - bloodstream (15%),
  - urinary tract (14%)
- Isolated organisms :
  - 62% were gram-negative bacteria
  - 47% were gram-positive bacteria,
  - 19% were fungi.

Vincent JL, et al. International study of prevalence and outcome of infection in intensive care unit. JAMA 2009;302(21):2323-9

Surviving Sepsis Campaign Bundles

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

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply **vasopressors** (for hypotension that does not respond to initial fluid resuscitation) to maintain a MAP ≥65 mmHg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L :
   - Measure **CVP**
   - Measure **$ScvO_2$**
7) **Remeasure lactate** if initial lactate was elevated

Surviving Sepsis Campaign

- The Surviving Sepsis Campaign Bundle: 2018 update

Intensive Care Med (2021) 47:1181–1247
https://doi.org/10.1007/s00134-021-06506-y

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Laura Evans[1*], Andrew Rhodes[2], Waleed Alhazzani[3], Massimo Antonelli[4], Craig M. Coopersmith[5], Craig French[6], Flávia R. Machado[7], Lauralyn Mcintyre[8], Marlies Ostermann[9], Hallie C. Prescott[10],

- Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Sepsis and septic shock are major healthcare problems, impacting millions of people around the world each year and killing between one in three and one in six of those it affects.
- Early identification and appropriate management in the initial hours after the development of sepsis improve outcomes.

Screening and early treatment

- Sepsis performance improvement programmes generally consist of sepsis screening, education, measurement of sepsis bundle performance, patient outcomes, and actions for identifed opportunities.
- Perform improvement programme, Sepsis screening, SOP

Recommendation
1. For hospitals and health systems, we **recommend** using a performance improvement programme for sepsis, including sepsis screening for acutely ill, high-risk patients and standard operating procedures for treatment
Strong recommendation, moderate quality of evidence for screening
Strong recommendation, very low-quality evidence for standard operating procedures

Tools are used for sepsis screening

- Systemic Infammatory Response Syndrome (SIRS) criteria,
- Quick Sequential Organ Failure Score (qSOFA)
- Sequential Organ Failure Assessment (SOFA) criteria,
- National Early Warning Score (NEWS),
- Modifed Early Warning Score (MEWS)

Recommendation
2. We **recommend against** using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock *Strong recommendation, moderate-quality evidence*

Recommendation
3. For adults suspected of having sepsis, we **suggest** measuring blood lactate *Weak recommendation, low-quality evidence*

Screening tool

- SIRS
- NEWS
- MEWS

- Against qSOFA

Initial resuscitation

Recommendations
4. Sepsis and septic shock are medical emergencies, and we **recommend** that treatment and resuscitation begin immediately *Best Practice Statement*
5. For patients with sepsis induced hypoperfusion or septic shock we **suggest** that at least 30 mL/kg of intravenous (IV) crystalloid fluid should be given within the first 3 h of resuscitation *Weak recommendation, low-quality evidence*

- Resuscitation immediately
- 30 mL/kg IV Crystalloid, within 3H

6. For adults with sepsis or septic shock, we **suggest** using dynamic measures to guide fluid resuscitation, over physical examination or static parameters alone

Weak recommendation, very low-quality evidence

Remarks

Dynamic parameters include response to a passive leg raise or a fluid bolus, using stroke volume (SV), stroke volume variation (SVV), pulse pressure variation (PPV), or echocardiography, where available

7. For adults with sepsis or septic shock, we **suggest** guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate

Weak recommendation, low-quality evidence

Remarks

During acute resuscitation, serum lactate level should be interpreted considering the clinical context and other causes of elevated lactate

8. For adults with septic shock, we **suggest** using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion

Weak recommendation, low-quality evidence

Dynamic parameters

- PLR
- SV
- SVV
- PPV
- Serum Lactate
- CRT

Mean arterial pressure

Recommendation
9. For adults with septic shock on vasopressors, we **recommend** an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets *Strong recommendation, moderate-quality evidence*

- MAP of 65 mmHg
- Admitting ICU within 6H

Admission to intensive care

Recommendation
10. For adults with sepsis or septic shock who require ICU admission, we **suggest** admitting the patients to the ICU within 6 h *Weak recommendation, low-quality evidence*

Infection

- Early administration of appropriate antimicrobials is one of the most effective interventions to reduce mortality in patients with sepsis.
- Delivering antimicrobials to patients with sepsis or septic shock should therefore be treated as an emergency.

[Original Research Critical Care]

CHEST

ED Door-to-Antibiotic Time and Long-term Mortality in Sepsis

Ithan D. Peltan, MD; Samuel M. Brown, MD; Joseph R. Bledsoe, MD; Jeffrey Sorensen, MStat; Matthew H. Samore, MD; Todd L. Allen, MD; and Catherine L. Hough, MD

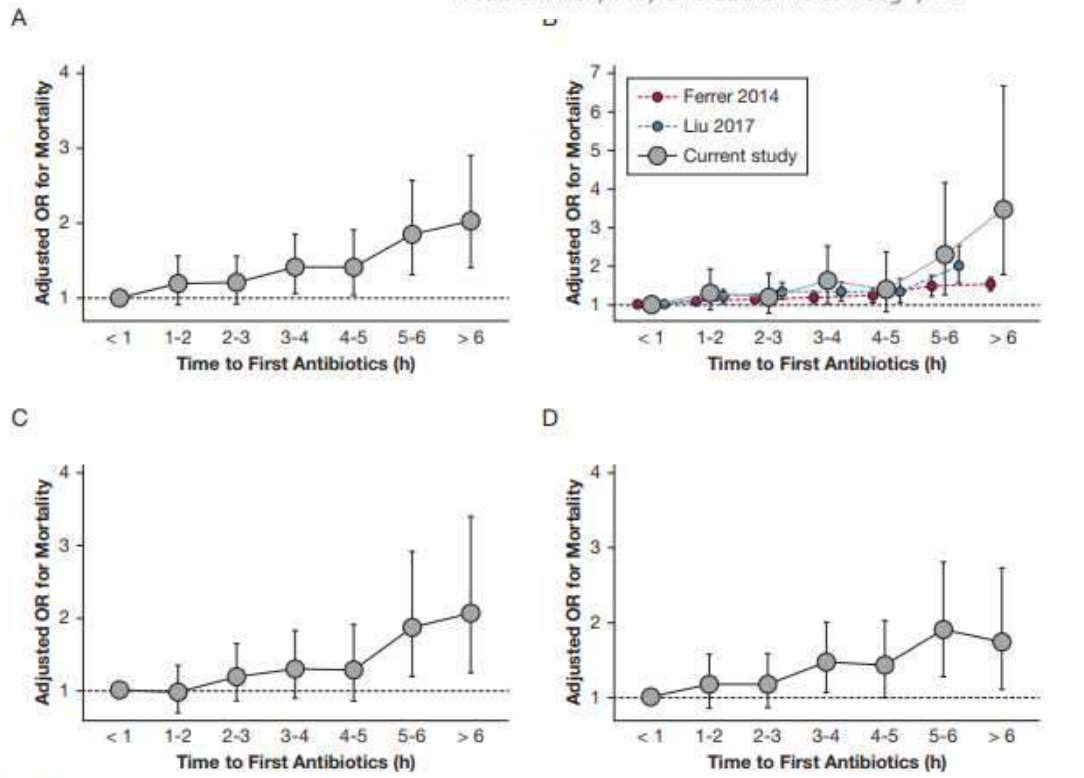


Figure 2 – *Adjusted association of mortality with door-to-antibiotic time, comparing each hourly interval following the first hour to door-to-antibiotic time ≤ 1 h for (A) 1-year mortality, (B) hospital mortality, (C) 30-day mortality, and (D) 90-day mortality. For hospital mortality, results from the current analysis are compared with risk-adjusted associations with hospital mortality reported by Ferrer et al[9] and Liu et al.[10] Figure adapted with permission of the American Thoracic Society from Liu et al[10] and with permission from Elsevier from Peltan and Liu.[34] The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.*

Characteristic	N	Adjusted OR (95% CI)	*P* Value
Overall	10,811	1.10 (1.05-1.14)	< .001
High acuity score	5,735	1.11 (1.06-1.17)	.37
Low acuity score	5,076	1.08 (1.02-1.14)	
Hypotension	874	1.13 (1.00-1.28)	.57
No hypotension	9,937	1.09 (1.05-1.13)	
MEDS score 3-5	2,068	1.10 (1.02-1.19)	.77
MEDS score 2	3,120	1.11 (1.04-1.18)	
MEDS score 1	5,623	1.08 (1.02-1.14)	
Altered mental status	561	1.14 (0.98-1.32)	.58
Intact mental status	10,250	1.09 (1.05-1.14)	
Initial lactate > 2 mmol/L	3,860	1.10 (1.04-1.17)	.76
Initial lactate ≤ 2 mmol/L	6,951	1.09 (1.04-1.14)	
Female	5,972	1.12 (1.06-1.18)	.19
Male	4,839	1.07 (1.02-1.13)	

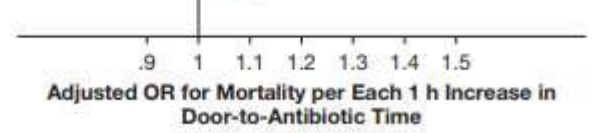


Figure 3 – *Variation in the adjusted association of door-to-antibiotic time and 1-year mortality according to patient and clinical factors. Mortality in Emergency Department Sepsis.*

- CHEST 2019; 155(5):938-946

- Among 10,811 eligible patients, median door-to-antibiotic time was 166 min, and 1-year mortality was 19%.
- Each additional hour from ED arrival to antibiotic initiation was associated with a 10% increased odds of 1-year mortality. The association remained linear when each 1-h interval of door-to-antibiotic time was independently compared with door-to-antibiotic time <1 h and was similar for hospital, 30-day, and 90-day mortality.
- Mortality at 1 year was higher when door-to-antibiotic times were > 3 h vs > 3 h but not > 1 h vs < 1 h (adjusted OR, 1.26; 95% CI, 0.98-1.62).
- CONCLUSIONS: Delays in ED antibiotic initiation time are associated with clinically important increases in long-term, risk-adjusted sepsis mortality.

Diagnosis of infection

Recommendation
11. For adults with suspected sepsis or septic shock but unconfirmed infection, we **recommend** continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected
Best Practice statement

- Continuously reevaluating, searching Dx.

Time to antibiotics

Recommendations
12. For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within 1 h of recognition
Strong recommendation, low quality of evidence (Septic shock)
Strong recommendation, very low quality of evidence (Sepsis without shock)
13. For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness
Best Practice Statement
Remarks
Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 h of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood of sepsis is thought to be high
14. For adults with possible sepsis without shock, we **suggest** a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 h from the time when sepsis was first recognised
Weak recommendation, very low quality of evidence

- Septic shock Antimicrobial within 1H
- Rapid assessment infectious
- Sepsis without shock Antimicrobial within 3H

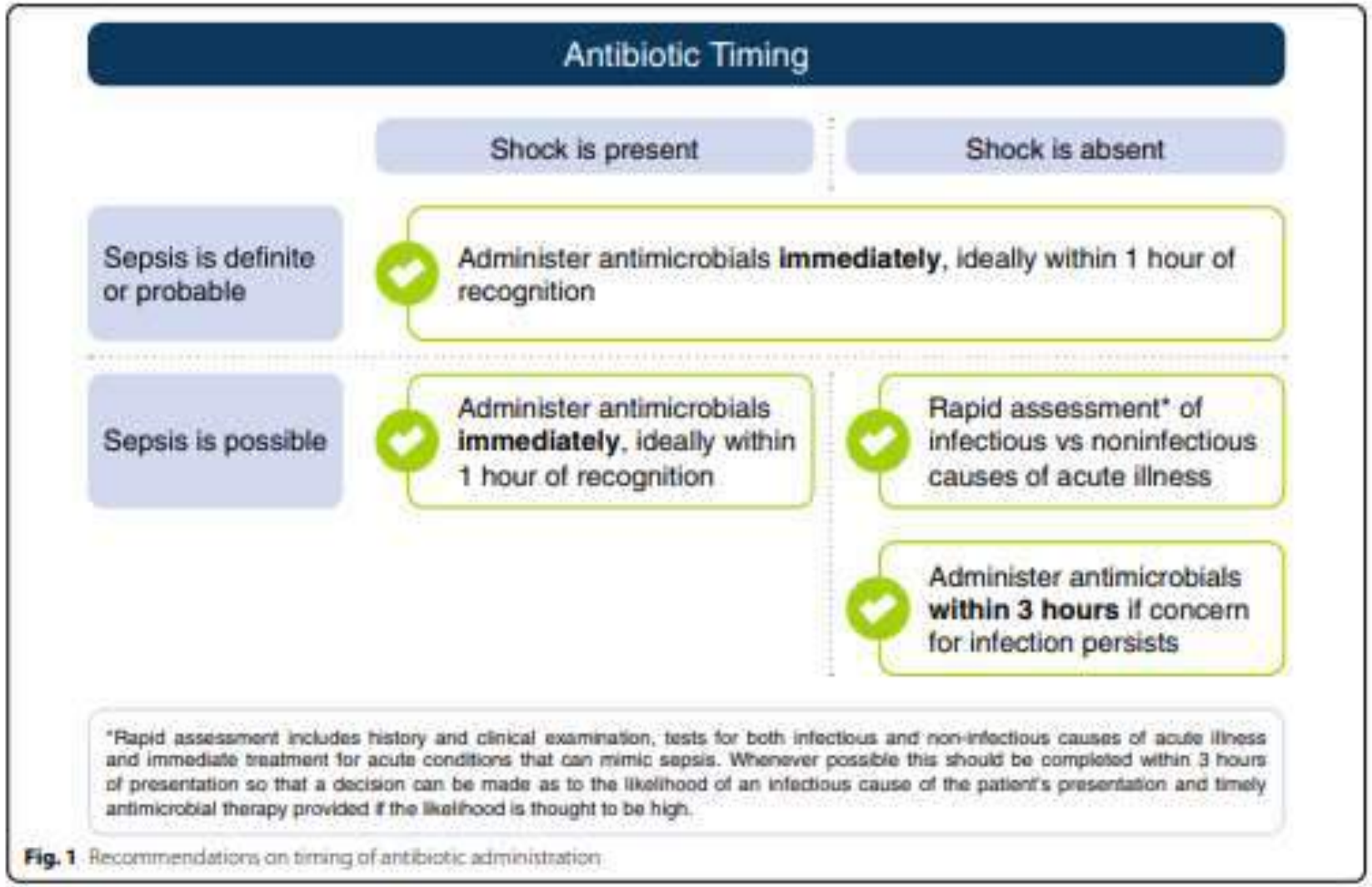
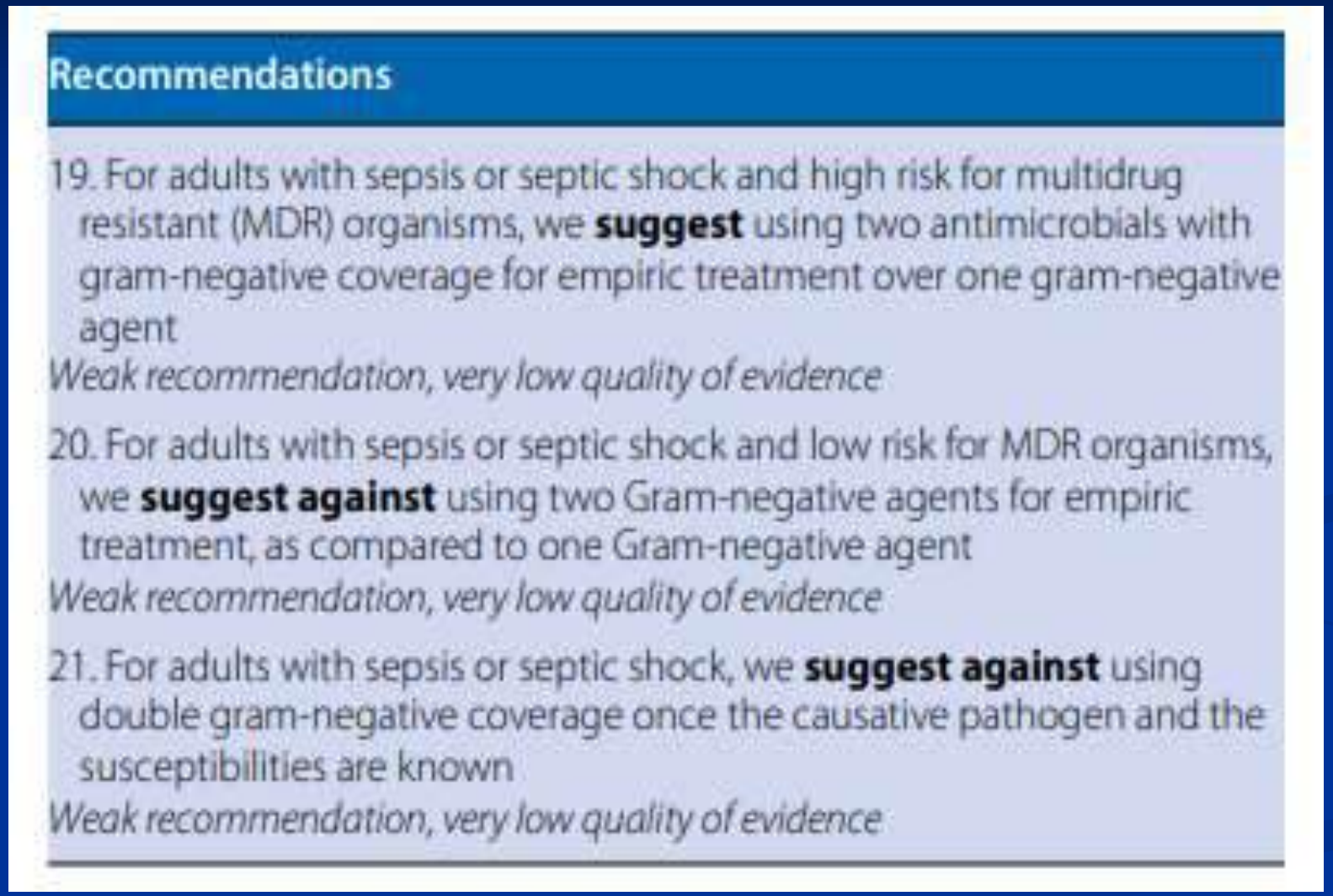


Fig. 1 Recommendations on timing of antibiotic administration

Antimicrobial choice

Recommendations
17. For adults with sepsis or septic shock at high risk of methicillin resistant staph aureus (MRSA), we **recommend** using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage *Best Practice statement*
18. For adults with sepsis or septic shock at low risk of methicillin resistant staph aureus (MRSA), we **suggest against** using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage *Weak recommendation, low quality of evidence*



Recommendations

19. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent

Weak recommendation, very low quality of evidence

20. For adults with sepsis or septic shock and low risk for MDR organisms, we **suggest against** using two Gram-negative agents for empiric treatment, as compared to one Gram-negative agent

Weak recommendation, very low quality of evidence

21. For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known

Weak recommendation, very low quality of evidence

- MDR; 2 antimicrob
- Low risk MDR against 2 am
- Against double gram negative once causative pathogen and susceptibilities are known

Antifungal therapy

Recommendations
22. For adults with sepsis or septic shock at high risk of fungal infection, we **suggest** using empiric antifungal therapy over no antifungal therapy *Weak recommendation, low quality of evidence*
23. For adults with sepsis or septic shock at low risk of fungal infection, we **suggest against** empiric use of antifungal therapy *Weak recommendation, low quality of evidence*

Antiviral therapy

Recommendation
24. We make **no recommendation** on the use of antiviral agents

Delivery of antibiotics

Recommendation
25. For adults with sepsis or septic shock, we **suggest** using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion *Weak recommendation, moderate quality of evidence*

Pharmacokinetics and pharmacodynamics

Recommendation
26. For adults with sepsis or septic shock, we **recommend** optimising dosing strategies of antimicrobials based on accepted pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties *Best Practice Statement*

Source control

- Appropriate is a key principle in the management of sepsis and septic shock.
- Source control may include drainage of an abscess, debriding infected necrotic tissue, removal of a potentially infected device, or definitive control of a source of ongoing microbial contamination.
- Source control should be achieved as soon as possible following initial resuscitation.

Source control

Recommendation
27. For adults with sepsis or septic shock, we **recommend** rapidly identifying or excluding a specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical
Best Practice Statement

Recommendation
28. For adults with sepsis or septic shock, 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
Best Practice Statement

- Emergent source control
- Removal of iv access possible source of sepsis

De-escalation of antibiotics

Recommendation
29 For adults with sepsis or septic shock, we **suggest** daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation *Weak recommendation, very low quality of evidence*

- Daily ass for de-escalation over fixed duration tx

Duration of antibiotics

Recommendation
30. For adults with an initial diagnosis of sepsis or septic shock and adequate source control, we **suggest** using shorter over longer duration of antimicrobial therapy *Weak recommendation, very low quality of evidence*

Biomarkers to discontinue antibiotics

Recommendation
31. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we **suggest** using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone *Weak recommendation, low quality of evidence*

- Shorter duration am tx
- Optimal tx unclear using procalcitonin AND clin evaluation to discontinue am

Table 3 Guidance for PK/PD-based dosing for specific drug classes

Drug or drug class	PK/PD index associated with bacterial killing or efficacy	Drug concentration target	Considerations for optimised dosing[a]	References
Antibacterials				
Aminoglycosides	AUC_{0-24}/MIC; C_{max}/MIC	AUC 70–100 C_{max}/MIC 8–10	Use extended interval dosing with patient weight and kidney function	[237]
Beta-lactams	$fT_{>MIC}$	C_{min} > MIC	Use prolonged infusions, consider patient weight and kidney function	[253]
Colistin	AUC_{0-24}/MIC	Unspecified	Use patient weight and kidney function	[259]
Daptomycin	AUC_{0-24}/MIC; C_{max}/MIC	AUC_{0-24}/MIC > 200	Use patient weight and kidney function	[237]
Fluoroquinolones	AUC_{0-24}/MIC; C_{max}/MIC	AUC_{0-24}/MIC 80–125	Use kidney function	[237]
Vancomycin	AUC_{0-24}/MIC	AUC_{0-24}/MIC 400	Use patient weight and kidney function	[260]
Antifungals				
Fluconazole	AUC_{0-24}/MIC	AUC_{0-24}/MIC 100	Use patient weight and kidney function	[261]
Posaconazole	AUC_{0-24}/MIC	C_{min} 1–4 mg/L	Use formulation-specific dose	[261]
Voriconazole	AUC_{0-24}/MIC	C_{min} 2–6 mg/L	Use patient weight	[261]

AUC_{0-24} ratio of area under the concentration–time curve from 0 to 24 h, *MIC* minimum inhibitory concentration, *$fT_{>MIC}$* time overdosing interval that free (unbound) drug is maintained above the MIC, *C_{max}* maximum concentration in a dosing interval, *C_{min}* minimum concentration in a dosing interval

[a] Other considerations than those listed may have been listed in studies in critically ill patient sub-populations

VAP, RISK MDR

TABLE 2. RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS CAUSING HOSPITAL-ACQUIRED PNEUMONIA, HEALTHCARE-ASSOCIATED PNEUMONIA, AND VENTILATOR-ASSOCIATED PNEUMONIA

- Antimicrobial therapy in preceding 90 d
- Current hospitalization of 5 d or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

The VAP bundle

1. Elevation of the head of the bed (HOB)
2. Daily sedation vacations and assessment of readiness to extubate
3. Peptic ulcer disease prophylaxis
4. Deep vein thrombosis (DVT) prophylaxis
5. Daily oral care with chlorhexidine (added in 2010)

AACN Advanced Critical Care Volume 25 , Number 2 , pp. 163 – 175

Initial Empiric Therapy (Doses)

Antipseudomonal cephalosporin

- Cefepime – 1-2 g Q8-12h
- Ceftazidime – 2g Q8h

Carbapenem

- Imipenem – 500 mg Q6h or 1g Q8h
- Meropenem – 1g Q8h

β-lactam/inhibitor

- Pip/tazo – 4.5g Q6h

Antipseudomonal FQ

- Levofloxacin – 750 mg Q24h
- Ciprofloxacin – 400 mg Q8h

Aminoglycoside

- Gentamicin – 7 mg/kg Q24h
- Tobramycin – 7 mg/kg Q24h
- Amikacin – 20mg/kg Q24h

ORSA Coverage

- Vancomycin – 15mg/kg Q24h
- Linezolid – 600 mg Q12h

Summary

- Sepsis and septic shock are major healthcare problems.
- It requires prompt recognition, appropriate antibiotics, careful hemodynamic support, and control of the source of infection.
- Early identification and appropriate management in the initial hours after the development of sepsis improve outcomes.