



What's new : Surviving Sepsis Campaign 2021 Update and controversies.

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SEPSIS MANAGEMENT

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graph TD; A[SEPSIS MANAGEMENT] --> B[HEMODYNAMIC MANAGEMENT<br/>(SOSD paradigm)]; A --> C[MODULATION OF THE<br/>HOST RESPONSE]; A --> D[INFECTION MANAGEMENT]; B --> B1[• IV fluids]; B --> B2[• Vasoactive agents]; C --> C1[• Hydrocortisone?]; C --> C2[• Vasopressin?]; D --> D1[• Antibiotics]; D --> D2[• Source control];
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HEMODYNAMIC MANAGEMENT (SOSD paradigm)

- IV fluids
- Vasoactive agents

MODULATION OF THE HOST RESPONSE

- Hydrocortisone?
- Vasopressin?

INFECTION MANAGEMENT

- Antibiotics
- Source control

What's new in SSC 21

- 93 recommendations
- 20 new or different recommendations
- 14 strong recommendations
- 15 best practice recommendations

Definition of sepsis

- Against using qSOFA compare to NEWS or SIRS.

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

- q-SOFA score- more specific less sensitive from 2/4 SIRS for diagnosis of sepsis.
- Using Lactate for suspected sepsis- only a tool- alone- not specific and not sensitive.
- No ideal method for definition .
- Clinical decision of organ failure due to hypoperfusion

Fluid Resuscitation and vasopressor therapy

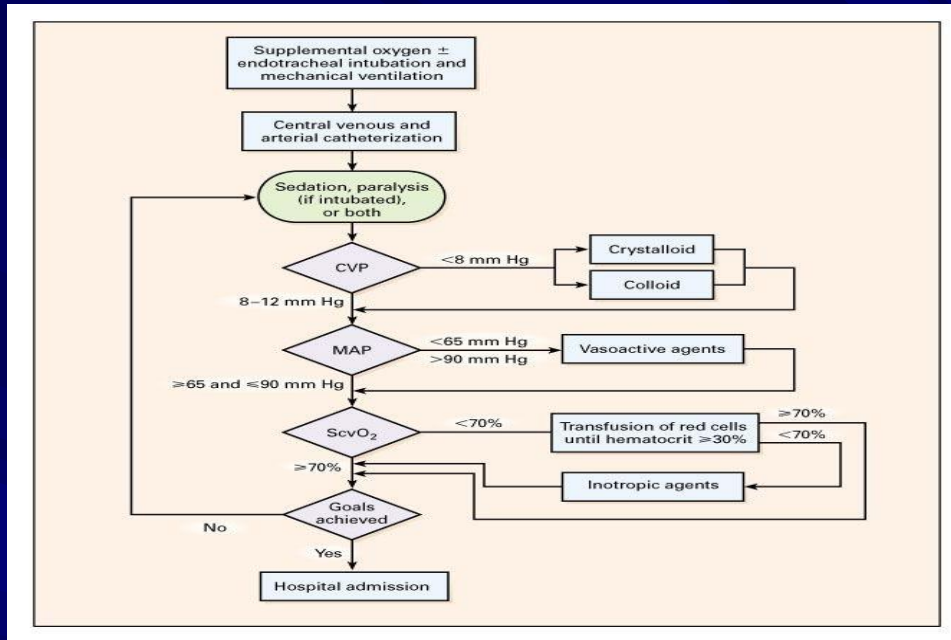
1. What are ideal endpoints for volume resuscitation and how volume resuscitation be treated? (Amount, timing, guiding clinical variables).

a. The rational-

- # Increase CO (early sepsis)
- # Increase microvascular perfusion in patient with septic shock
- # Improve organ function.

b. The optimal amount of fluid requirement –that restores perfusion to end organ while not worsening the end organ function –The bimodal influence of fluids: The U shape response curve.

- EGDT-failed in showing reduced mortality.



- **Positive fluid balance- increase mortality (Skar-CCM: 2018)**
- Meyhoff (Chest 2020) –limited vs.liberal -metanalysis 9 trials - no difference

Conclusion- individualization of fluid therapy is desired.

45 There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after the initial resuscitation.

2016 STATEMENT

1 "We **suggest** using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock."

1 "We **suggest** using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."







2. monitoring fluid resuscitation –

Dynamic variables (POCUS IVC compression) vs. static variables (CVP), Thermodilution CO.

Capillary refill time (CRT) - better than lactate (Andromeda-shock trial JAMA 2019) late in shock - reduce mortality.

Lactate as sign of hypoperfusion better early in shock.

Follow lactate clearance.

| | | |
|---|---|---|
|  |  VERY LOW | 6 For adults with sepsis or septic shock, we suggest using dynamic measures to guide fluid resuscitation, over physical examination, or static parameters alone. |
|  |  LOW | 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. |
|  |  LOW | 8 For adults with septic shock, we suggest using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion. |

3. Is early is better?

| 2005 | 2013 | 2018 |
|---|--|---|
| 6-hour Resuscitation Bundle <ul style="list-style-type: none"> • Measure serum lactate • Obtain blood cultures prior to antibiotics • Administer broad spectrum antibiotics within 3 hours of ED or 1 hour non-ED admission • With hypotension &/or serum lactate > 4 mmol/L: <ul style="list-style-type: none"> ○ Crystalloid 20ml/Kg ○ Vasopressors if unresponsive • Persistent hypotension &/or lactate > 4 mmol/L achieve: <ul style="list-style-type: none"> • CVP \geq 8 mm Hg • ScvO2 \geq 70 % or SvO2 \geq 65% | 3-hour Bundle <ul style="list-style-type: none"> • Measure serum lactate • Obtain blood cultures prior to antibiotics • Administer broad spectrum antibiotics • With hypotension &/or serum lactate > 4 mmol/L: <ul style="list-style-type: none"> ○ Crystalloid 30ml/Kg 6-hour Bundle <ul style="list-style-type: none"> • Vasopressors for hypotension after fluid • For persistent arterial hypotension after fluid or with lactate > 4 mmol/L; <ul style="list-style-type: none"> • Measure CVP • Measure ScvO2 | 1-hour Bundle <ul style="list-style-type: none"> • Measure serum lactate. Re-measure if initial > 2 mmol/L • Obtain blood cultures prior to antibiotics • Administer broad spectrum antibiotics • Begin rapid crystalloid 30 ml/kg • Apply vasopressors if hypotension remains after fluid resuscitation to MAP \geq 65 mm Hg |
| 24-hour Management Bundle <ul style="list-style-type: none"> • Low dose steroids • Human activated protein C (rhAPC) • Maintain glucose 70 -150 mg/dL • Maintain median inspiratory plateau pressure < 30 cm H2O in mechanical ventilation | 24-hour Bundle no longer recommended | |

INITIAL RESUSCITATION



BEST PRACTICE

4 Sepsis and septic shock are medical emergencies, and we **recommend** that treatment and resuscitation begin immediately.



LOW

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 hours of resuscitation.

2016 STATEMENT



*"We **recommend** that in the initial resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours."*

Beginning of fluids > 2 HR – increase mortality

Giving bolus in 1 hour bundle – no change in mortality (Seymour 2017 NEJM)

More than 5 in first day- increase in hospital mortality

What is the optimal fluid for sepsis resuscitation



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ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis



Naomi E. Hammond, Ph.D.^{1,2}, Fernando G. Zampieri, Ph.D.^{3,4}, Gian Luca Di Tanna, Ph.D.⁵, Tessa Garside, Ph.D.^{1,2}, Derick Adigbli, Ph.D.^{1,2}, Alexandre B. Cavalcanti, M.D. Ph.D.³, Flavia R. Machado, M.D., Ph.D.⁶, Sharon Micallef, B.N.¹, John Myburgh, Ph.D.^{1,7}, Mahesh Ramanan, M.Med.^{8,9}, Todd W. Rice, M.D.¹⁰, Matthew W. Semler, M.D.¹⁰, Paul J. Young, Ph.D.^{11,12}, Balasubramanian Venkatesh, M.D.^{1,13}, Simon Finfer, M.D.^{1,14}, and Anthony Delaney, Ph.D.^{1,2}

Drs. Hammond and Zampieri, as well as Drs. Finfer and Delaney, contributed equally to this article.

CONCLUSIONS The estimated effect of using balanced crystalloids versus saline in critically ill adults ranges from a 9% relative reduction to a 1% relative increase in the risk of death, with a high probability that the average effect of using balanced crystalloids is to reduce mortality. (PROSPERO number, CRD42021243399.)



| Composition/properties | Human plasma | Solutions | | | | | Plasma-Lyte |
|------------------------|--------------|-------------|-------------------|---------------------|------------------|------------------|-------------|
| | | 0.9% saline | Ringer's solution | Hartmann's solution | Ringer's lactate | Ringer's acetate | |
| pH | 7.35 - 7.45 | 5.5 | 6.0 | 6.5 | 6.5 | 6.7 | 7.4 |
| Osmolality (mOsm/L) | 291 | 308 | 310 | 279 | 273 | 270 | 294 |
| Sodium (mmol/L) | 135 - 145 | 154 | 147 | 131 | 130 | 131 | 140 |
| Potassium (mmol/L) | 4.5 - 5.5 | | 4 | 5 | 4 | 4 | 5 |
| Calcium (mmol/L) | 2.2 - 2.6 | | 2.2 | 2 | 1.5 | 2 | |
| Magnesium (mmol/L) | 0.8 - 1.0 | | | | | 1 | 1.5 |
| Chloride (mmol/L) | 94 - 111 | 154 | 156 | 111 | 109 | 110 | 98 |
| Bicarbonate (mmol/L) | 23 - 27 | | | | | | |
| Lactate (mmol/L) | 1.0 - 2.0 | | | 29 | 28 | | |
| Acetate (mmol/L) | | | | | | 30 | 27 |
| Gluconate (mmol/L) | | | | | | | 23 |

- Ringer lactate-**SMART Trial** (NEJM 2018) -decrease mortality 1 death /94 ICU patients .More prominence in septic patients.
- Reduced RRT, persistent renal injury.
- **SALT-ED Trial** (NEJM 2018) –in non critical ill patients- found no difference in mortality and RRT.

MODERATE


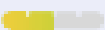
32 For adults with sepsis or septic shock, we **recommend** using crystalloids as first-line fluid for resuscitation.

LOW

33 For adults with sepsis or septic shock, we **suggest** using balanced crystalloids instead of normal saline for resuscitation.

2016 STATEMENT

"We **suggest** using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock"

- **Role of Albumin?** –SAFE Trial- NEJM 2004-In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.-
- ALBIOS Trial –Caironi- NEJM 2014- In patients with severe sepsis, albumin replacement in addition to crystalloids, as compared with crystalloids alone, **did not improve the rate of survival at 28 and 90 days.**
survival benefit of albumin therapy in patients who started therapy 6–24 h after onset of sepsis compared to those who started it earlier.
In the 1121 patients with septic shock, 90-day mortality was lower in the albumin group (564 patients) than in the NON- albumin group (43.6 vs. 49%, $p = 0.03$)



MODERATE

34

For adults with sepsis or septic shock, we **suggest** using albumin in patients who received large volumes of crystalloids.

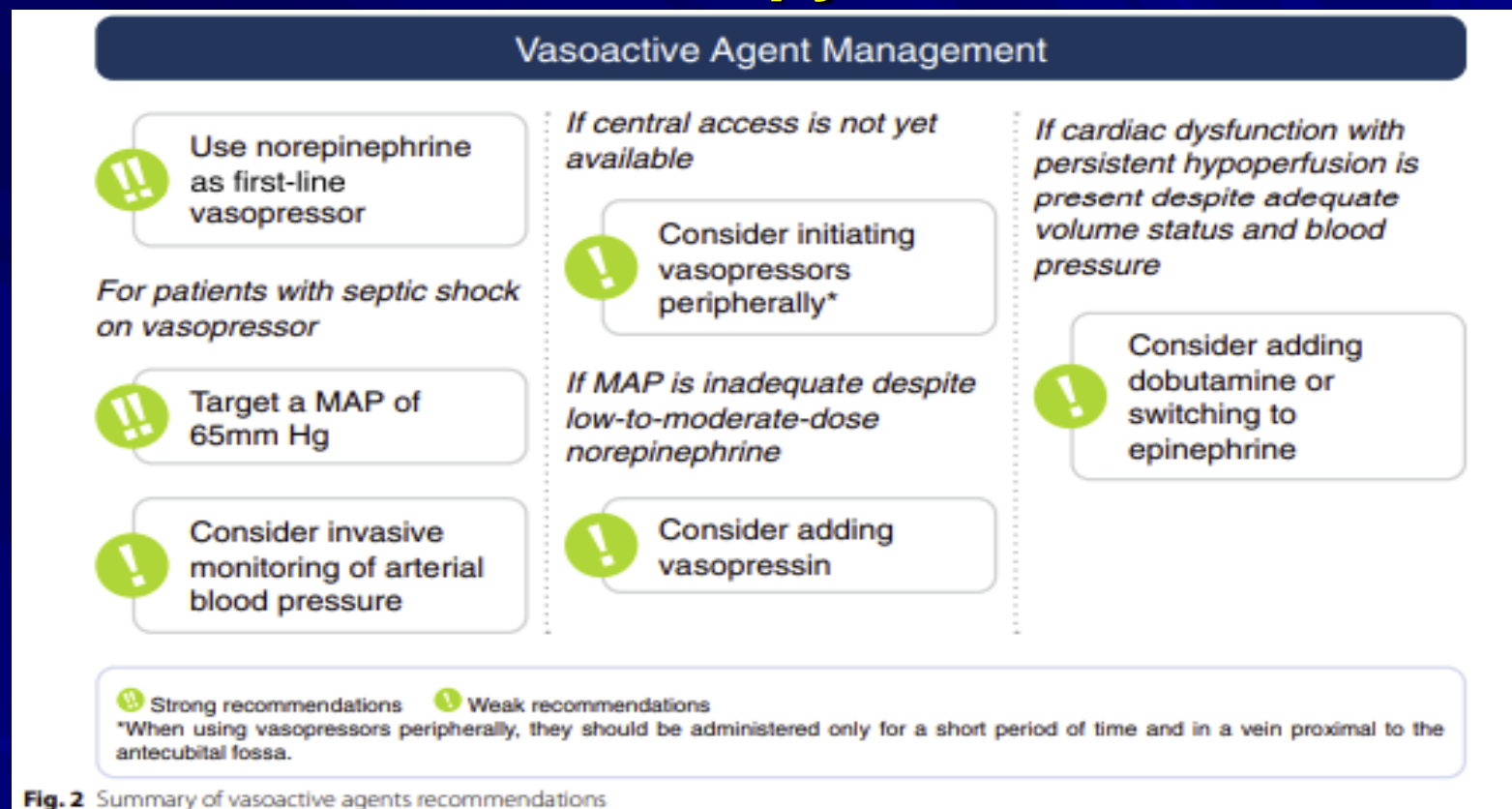


HIGH

35

For adults with sepsis or septic shock, we **recommend against** using starches for resuscitation.

What is the optimal Approach to selection, dose titration and escalation of vasopressor therapy?



VERY LOW



For adults with septic shock, we **suggest** starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured.

Is There a Good MAP for Septic Shock?

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

SepsisSpam trial(NEJM 2014) -no difference in 80-85mmHg in 29/90 days mortality .

% More mortality if treated with pressors for 80-85 for more then 6 hours.

Depend in chronic hypertension (Autoregulation shift of BBB)

Bicarbonate therapy ?

Bicarbonate therapy

Recommendations

71. For adults with septic shock and hypoperfusion-induced lactic acidemia, we **suggest against** using sodium bicarbonate therapy to improve haemodynamics or to reduce vasopressor requirements
Weak recommendation, low quality of evidence

72. For adults with septic shock, severe metabolic acidemia ($\text{pH} \leq 7.2$) and AKI (AKIN score 2 or 3), we **suggest** using sodium bicarbonate therapy

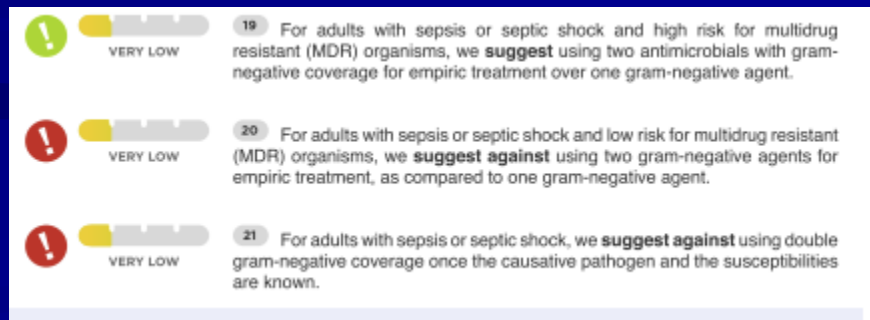
Weak recommendation, low quality of evidence

Open questions?

1. what should the starting dose of Norepinephrine be?
2. when should patients received fluid resuscitation vs. vasopressor initiation vs. both?

Infection-Source control

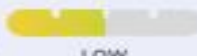
- Suspected Sepsis with septic shock – give broad spectrum AB in less than 1 hour
- Possible Sepsis without shock- rapid investigation for infection and non- infectious acute illness – give AB in 3 hours.
- Low risk for sepsis without shock - assess! - do not treat with AB
- Septic shock with high risk MDR gram negative- give 2 AB
- Beta lactams should be given as continuous infusion, results in sustained concentrations which align with the pharmacodynamics of these drugs.





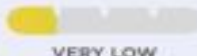
BEST PRACTICE

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.



LOW

Septic shock



VERY LOW

Sepsis without shock

2016 STATEMENT



"We **recommend** that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."



BEST PRACTICE

13 For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness.



VERY LOW

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 hours from the time when sepsis was first recognized.

2016 STATEMENT



"We **recommend** that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."



VERY LOW

15 For adults with a low likelihood of infection and without shock, we **suggest** deferring antimicrobials while continuing to closely monitor the patient.

2016 STATEMENT



"We **recommend** that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."

Steroids in sepsis

- ADRENAL Trial- NEJM 2018- no change in mortality in 90 days.
- APROCCHSS Trial-Annane NEJM 2018 –mild mortality reduction in 90 days.
- Metanalysis 37 RCT 9500 patients- Pang ,JAMA 2018 -corticosteroids is associated with reduced 28-day mortality compared with placebo use or standard supportive.
- Metanalysis 42 RCT 10194 patients- Rochwerg-CCM 2019-In critically ill patients with sepsis, corticosteroids possibly result in a small reduction(1/8% absolute reduction) in mortality while also possibly increasing the risk of neuromuscular weakness.
- **More freedom in using mineralocorticoids in vasopressor dependent**

ADDITIONAL THERAPIES

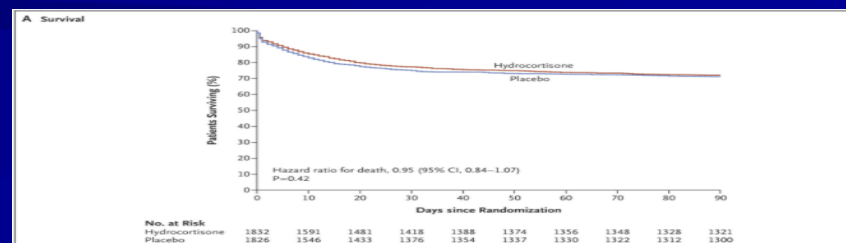
MODERATE

58 For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids.

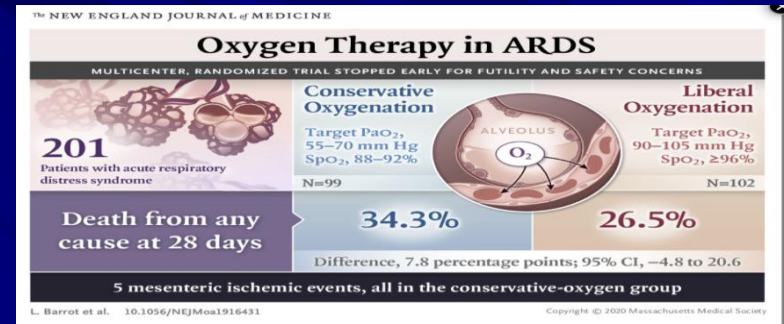
2016 STATEMENT

↑ **1** **2** **3** **4** **5** **6** **7** **8** **9** **10**

*"We suggest **against** using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, we **suggest** intravenous hydrocortisone at a dose of 200 mg per day."*



Ventilation



a. Oxygen Target :

- # Among patients with ARDS, early exposure to a conservative-oxygenation strategy with a PaO₂ between 55 and 70 mm Hg did not increase survival at 28 D
- # No agreement about the optimal oxygen percentage-conservative- 88-92 or liberal >96%.

Oxygen targets

Recommendation

46. There is **insufficient evidence to make a recommendation** on the use of conservative oxygen targets in adults with sepsis-induced hypoxemic respiratory failure

b. High Flow- Nasal Treatment -HFNT

- New strategy for hypoxemic respiratory failure-AIRVO-2
- Benefits:
 1. maintenance of a constant FiO_2 .
 2. generation of a positive end-expiratory pressure (PEEP).
 3. reduction of the anatomical dead space.
 4. improvement of muco-ciliary clearance.
 5. reduction in the work of breathing.
 6. less face mask induces decubitus ulcer



- HFNC is **less effective at reducing work** of breathing than BIPAP and supplying a moderate or higher level of PEEP
- Frat -NEJM 2015 –
 1. primary outcome of **intubation rate at 28 days** was **not** different.
 2. **improved 90-day survival** with HFNC compared with NIV.
 3. HFNC patients experienced significantly **more days free of mechanical ventilation during a 28-day** study period.
 4. Main improvement- in sever hypoxemia
- Ni- Am J Emer Med- 2018 - nine RCTs showed that HFNC reduces intubation compared with conventional oxygen but **does not affect the risk of death or ICU length of stay.**



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For adults with sepsis-induced hypoxemic respiratory failure, we suggest the use of high flow nasal oxygen over non-invasive ventilation.

Extend Usages:

1. Effective for post- extubation compromise- reduced re-intubations.
2. Ventilation support modality in end of life.
3. Prevent early intubation in severe Covid -19 patients with ARDS .

תודה על ההקשבה

