**International Guidelines for Management of Sepsis and Septic Shock**

**Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2021**

**Appendix 1. Screening and Early Treatment**

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Table of Contents

[1. In acutely ill patients should we use a standardized screening process for sepsis (versus not)? 5](#_Toc59037365)

[Forest plot for Mortality 5](#_Toc59037366)

[Evidence profile: Standardized screening process in acutely ill patients 5](#_Toc59037367)

[EtD: Summary of judgements for the standardized screening process recommendation 10](#_Toc59037368)

[Type of Recommendation 10](#_Toc59037369)

[2. In patients with sepsis, should hospitals adopt standard operating procedures for treatment (versus no specific procedures)? 11](#_Toc59037370)

[Forest plot for Mortality: Early Goal Directed Therapy 11](#_Toc59037371)

[Evidence profile: standard operating procedures compared to no standard operating procedures for sepsis 12](#_Toc59037372)

[EtD: Summary of judgements for the standard operating procedures 13](#_Toc59037373)

[Type of Recommendation 14](#_Toc59037374)

[3. In acutely ill patients should we use qSOFA criteria to screen for the presence of sepsis? 14](#_Toc59037375)

[Evidence profile: qSOFA versus SIRS to screen for sepsis 14](#_Toc59037376)

[Evidence profile: qSOFA versus MEWS to screen for sepsis 15](#_Toc59037377)

[Evidence profile: qSOFA versus SOFA to screen for sepsis 15](#_Toc59037378)

[EtD: Summary of judgements for the standardized screening process recommendation 16](#_Toc59037379)

[Type of Recommendation 17](#_Toc59037380)

[4. In patients with suspected sepsis or septic shock should we use serum lactate to screen for sepsis? 17](#_Toc59037381)

[Forest plot for sensitivity and specificity 17](#_Toc59037382)

[Evidence profile: serum lactate to screen for sepsis 18](#_Toc59037383)

[EtD: Summary of judgements for the lactate to screen for sepsis recommendation 18](#_Toc59037384)

[Type of Recommendation 19](#_Toc59037385)

[5. In patients with known or suspected infection and hypotension and / or an elevated lactate should we administer 30mL/Kg BW of crystalloids or a rapid small volume fluid challenge and re-assess? 20](#_Toc59037386)

[EtD: Summary of judgements for the 30 ml/kg BW recommendation 20](#_Toc59037387)

[Type of Recommendation 21](#_Toc59037388)

[6. In hypotensive patients with known or suspected sepsis or septic shock should dynamic response (SV, SVV, PPV, echo) to fluid boluses or straight leg raise guide initial fluid resuscitation? 21](#_Toc59037389)

[Evidence profile: dynamic response (SV, SVV, PPV, echo) to fluid boluses or straight leg raise compared to control 21](#_Toc59037390)

[EtD: Summary of judgements for the dynamic response (SV, SVV, PPV, echo) to fluid boluses or straight leg raise 23](#_Toc59037391)

[Type of Recommendation 24](#_Toc59037392)

[7. In patients with suspected sepsis or septic shock, should fluid resuscitation be guided by physical examination, static or dynamic parameters? 24](#_Toc59037393)

[Evidence profile: physical examination, static or dynamic parameters to guide fluid resuscitation 24](#_Toc59037394)

[EtD: Summary of judgements for the dynamic response (SV, SVV, PPV, echo) to fluid boluses or straight leg raise 25](#_Toc59037395)

[Type of Recommendation 26](#_Toc59037396)

[8. In patients with sepsis and increased serum lactate, should lactate decrease be considered a target of initial sepsis resuscitation? 26](#_Toc59037397)

[Evidence profile: lactate decrease as target for initial resuscitation 26](#_Toc59037398)

[EtD: Summary of judgements for lactate decrease as a target of initial sepsis resuscitation 29](#_Toc59037399)

[Type of Recommendation 30](#_Toc59037400)

[9. In patients with known or suspected sepsis or septic shock should we target a mean arterial pressure of ≥ 65 mm Hg? 30](#_Toc59037401)

[Evidence profile: targeting MAP ≥65 mmHg 30](#_Toc59037402)

[EtD: Summary of judgements for targeting MAP ≥65 mmHg 32](#_Toc59037403)

[Type of Recommendation 33](#_Toc59037404)

[10. In patients with known or suspected sepsis or septic shock, should we admit to ICU in less than 6 hours? 33](#_Toc59037405)

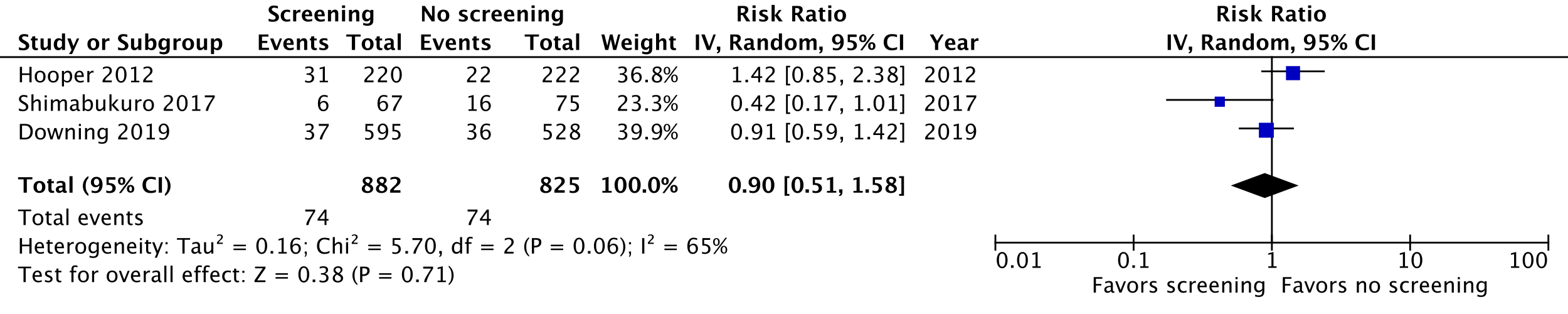
[Evidence profile: admission to ICU in < 6 hours 33](#_Toc59037406)

[EtD: Summary of judgements for admission to ICU in < 6 hours 35](#_Toc59037407)

[Type of Recommendation 36](#_Toc59037408)

# In acutely ill patients should we use a standardized screening process for sepsis (versus not)?

## Forest plot for Mortality



## 

## Evidence profile: Standardized screening process in acutely ill patients

**Setting:** critically ill patients

**Bibliography**: Warttig S, Alderson P, Evans DJW, Lewis SR, Kourbeti IS, Smith AF. Automated monitoring compared to standard care for the early detection of sepsis in critically ill patients. Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD012404. DOI: 10.1002/14651858.CD012404.pub2

| Quality assessment | | | | | | | № of patients | | Effect | | Quality | Importance |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | standardized screening process | No standardized process | Relative (95% CI) | Absolute (95% CI) |
| Mortality - short-term | | | | | | | | | | | | |
| 3 | **randomised trials** | **not serious** | **not serious** | **not serious a** | **serious b** | **none** | **74/882 (8.4%)** | **74/825 (9.0%)** | RR 0.90 **(0.51 to 1.58)** | **9 fewer per 1,000 (from 44 fewer to 52 more)** | **⨁⨁⨁◯ MODERATE** | **CRITICAL** |
| ICU LOS (assessed with: days) | | | | | | | | | | | | |
| 2 | **randomised trials** | **not serious** | **serious c** | **serious a** | **serious d** | **none** | **287** | **297** | **-** | **MD** 1.05 days lower **(0.31 lower to 1 higher)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| Antibiotics order - RCT | | | | | | | | | | | | |
| 2 | **randomised trials** | **not serious** | **not serious** | **not serious** | **serious e** | **none** | **239/662 (36.1%)** | **233/603 (38.6%)** | RR 0.91 **(0.72 to 1.14)** | **35 fewer per 1,000 (from 108 fewer to 54 more)** | **⨁⨁⨁◯ MODERATE** | **CRITICAL** |
| Lactate orders - RCT | | | | | | | | | | | | |
| 1 | **randomised trials** | **not serious** | **not serious** | **serious f** | **very serious g** | **none** | **84/595 (14.1%)** | **57/528 (10.8%)** | OR 1.36 **(0.95 to 1.94)** | **33 more per 1,000 (from 5 fewer to 82 more)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| Blood cultures orders -RCT | | | | | | | | | | | | |
| 1 | **randomised trials** | **not serious** | **not serious** | **serious h** | **very serious g** | **none** | **22/67 (32.8%)** | **30/75 (40.0%)** | OR 0.73 **(0.37 to 1.46)** | **73 fewer per 1,000 (from 202 fewer to 93 more)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| IV fluids order - RCT | | | | | | | | | | | | |
| 1 | **randomised trials** | **not serious** | **not serious** | **not serious** | **serious** | **none** | **141/595 (23.7%)** | **105/528 (19.9%)** | OR 1.25 **(0.94 to 1.66)** | **38 more per 1,000 (from 10 fewer to 93 more)** | **⨁⨁⨁◯ MODERATE** | **CRITICAL** |
| Antibiotics order | | | | | | | | | | | | |
| 3 | **observational studies** | **serious i** | **not serious** | **not serious** | **not serious** | **strong association** | **157/687 (22.9%)** | **140/826 (16.9%)** | OR 1.61 **(1.22 to 2.14)** | **78 more per 1,000 (from 30 more to 134 more)** | **⨁⨁◯◯ LOW** | **CRITICAL** |
| Lactate orders | | | | | | | | | | | | |
| 3 | **observational studies** | **serious i** | **not serious** | **serious f** | **not serious** | **strong association** | **541/3491 (15.5%)** | **233/3523 (6.6%)** | OR 2.64 **(1.89 to 3.70)** | **91 more per 1,000 (from 52 more to 141 more)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| Blood cultures orders | | | | | | | | | | | | |
| 2 | **observational studies** | **serious** | **not serious** | **serious h** | **serious j** | **none** | **139/598 (23.2%)** | **104/645 (16.1%)** | OR 1.64 **(1.20 to 2.24)** | **78 more per 1,000 (from 26 more to 140 more)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| IV fluids order | | | | | | | | | | | | |
| 2 | **observational studies** | **serious i** | **serious k** | **not serious** | **very serious l** | **none** | **189/598 (31.6%)** | **117/645 (18.1%)** | OR 3.56 **(0.91 to 13.92)** | **260 more per 1,000 (from 14 fewer to 574 more)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| Time to antibiotics - RCT (assessed with: hours) | | | | | | | | | | | | |
| 1 | **randomised trials** | **not serious** | **not serious** | **not serious** | **serious d** | **none** | **220** | **222** | **-** | **MD** 0.1 hours fewer **(3.06 fewer to 2.86 more)** | **⨁⨁⨁◯ MODERATE** | **CRITICAL** |
| Time to antibiotics (assessed with: hours) | | | | | | | | | | | | |
| 2 | **observational studies** | **serious i** | **not serious** | **not serious** | **not serious** | **none** | **83** | **77** | **-** | **MD** 1.5 hours fewer **(2.84 fewer to 0.16 fewer)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| Time to lactate order (assessed with: hours) | | | | | | | | | | | | |
| 1 | **observational studies** | **serious i** | **not serious** | **serious f** | **serious m** | **none** | **30** | **30** | **-** | **MD** 38.1 lower **(54.29 lower to 21.91 lower)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| Time to blood cultures (assessed with: hours) | | | | | | | | | | | | |
| 1 | **observational studies** | **serious i** | **not serious** | **serious h** | **very serious l** | **none** | **30** | **30** | **-** | **MD** 12.1 lower **(70.98 lower to 46.78 higher)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| Time to FLUIDS (assessed with: hours) | | | | | | | | | | | | |
| 1 | **observational studies** | **serious i** | **not serious** | **not serious** | **very serious l** | **none** | **30** | **30** | **-** | **MD** 5.2 lower **(22.43 lower to 12.03 higher)** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **OR:** Odds ratio

#### Explanations

a. We downgraded for indirectness by one point as population is includes only ICU patients.

b. We downgraded for imprecision by 2 points: confidence interval includes significant benefit and harm and small number of events < 300.

c. Significant heterogeneity detected (i2 = 100%)

d. We downgraded for imprecision by 1 point: confidence interval includes significant benefit and harm.

e. We downgraded for imprecision by 1 point as CI includes both significant benefit and harm.

f. While lactate order is part of the bundle, it is not a patient-important outcome.

g. We downgraded for imprecision by 2 points as confidence interval includes significant benefit and harm, small sample size as well as total events < 300

h. while part of the bundle, not a patient-important-outcome

i. 1 study at high risk of bias, all studies are before and after

j. We downgraded by 1 point for imprecision as total number of events is < 300

k. significant heterogeneity detected i2 85%

l. we downgraded for imprecision by 2 points as CI includes both significant benefits and harms and very wide CI

m. We downgraded for imprecision by 1 point for very small number of patients, total 60 and wide confidence intervals.

## **EtD:** Summary of judgements for the standardized screening process recommendation

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | Varies | **Don't know** |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

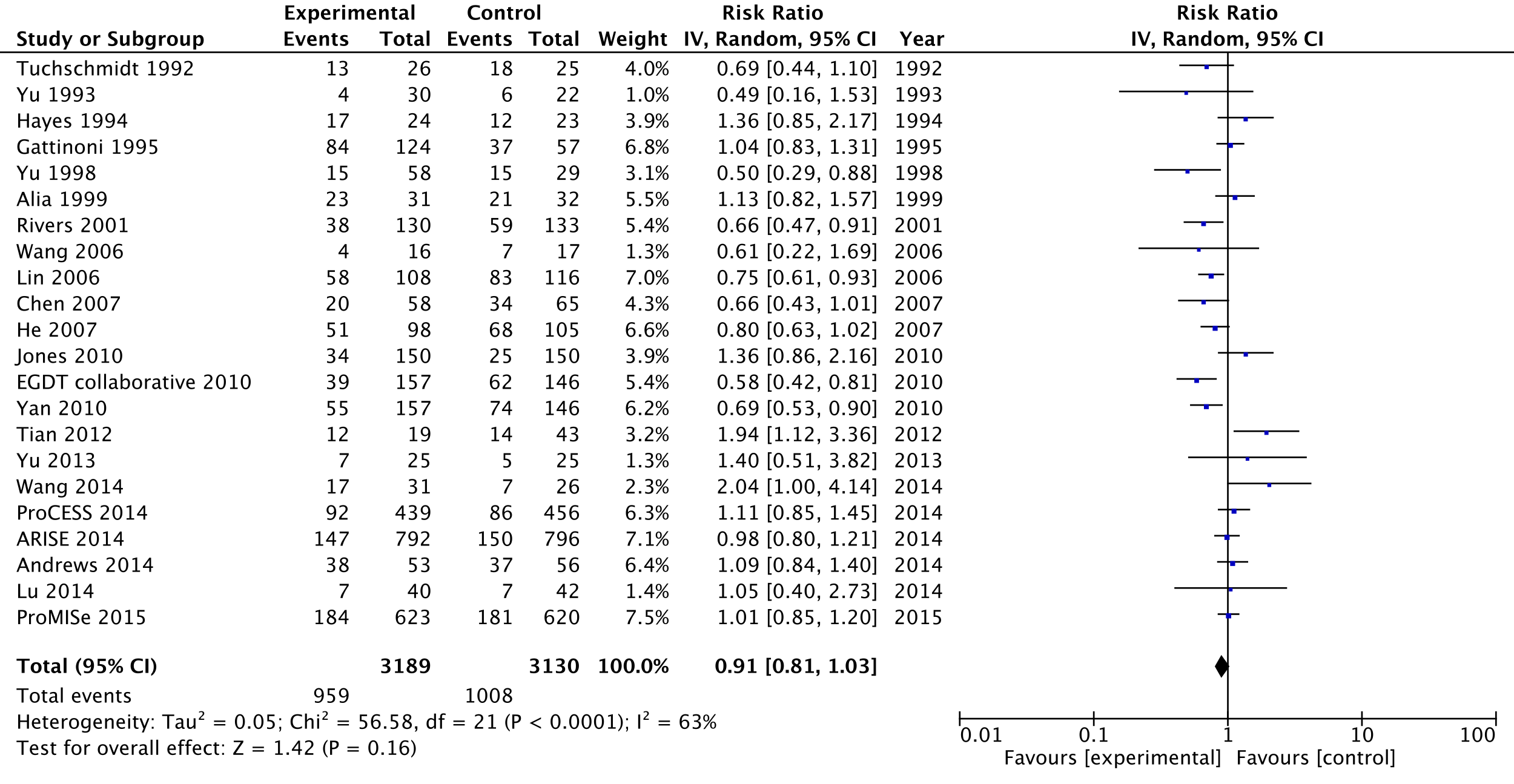
## Type of Recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | **Strong recommendation for the intervention** |
| ○ | ○ | ○ | ○ | **●** |

# 

# In patients with sepsis, should hospitals adopt standard operating procedures for treatment (versus no specific procedures)?

## Forest plot for Mortality: Early Goal Directed Therapy



## Evidence profile: standard operating procedures compared to no standard operating procedures for sepsis

**Setting**: critically ill patients

**Bibliography**: Damiani E, Donati A, Serafini G, Rinaldi L, Adrario E, Pelaia P, Busani S, Girardis M. Effect of performance improvement programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. PLoS One. 2015 May 6;10(5):e0125827. doi: 10.1371/journal.pone.0125827.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **standard operating procedures** | **no standard operating procedures** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| **22** | **randomised trials** | **not serious** | **serious a** | **not serious** | **not serious b** | **none** | **959/3189 (30.1%)** | **1008/3130 (32.2%)** | **RR 0.91 (0.81 to 1.03)** | **29 fewer per 1,000 (from 61 fewer to 10 more)** | **⨁⨁⨁◯ MODERATE** | **CRITICAL** |
| **Mortality (assessed with: SOP )** | | | | | | | | | | | | |
| **43** | **observational studies** | **not serious** | **serious** | **not serious** | **not serious** | **none** | **0 cases 0 controls / exposed / unexposed** | | **OR 0.66 (0.61 to 0.72)** | **-** | **⨁◯◯◯ VERY LOW** | **CRITICAL** |
| **-** | **10.0%** | **32 fewer per 1,000 (from 37 fewer to 26 fewer)** |
| **-** | **30.0%** | **80 fewer per 1,000 (from 93 fewer to 64 fewer)** |

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

#### Explanations

a. Significant heterogeneity detected i2 = 63%

b. We downgraded by 1 point for imprecision as confidence interval includes both significant benefit and harm.

## **EtD:** Summary of judgements for the standard operating procedures

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | Varies | **Don't know** |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

## **Type of Recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | **Strong recommendation for the intervention** |
| ○ | ○ | ○ | ○ | **●** |

# In acutely ill patients should we use qSOFA criteria to screen for the presence of sepsis?

## Evidence profile: qSOFA versus SIRS to screen for sepsis

**Setting** : critically ill patients

**Pooled sensitivity qSOFA** : 0.47 (95% CI: 0.28 to 0.66) | **Pooled specificity qSOFA** : 0.93 (95% CI: 0.88 to 0.97)

**Pooled sensitivity SIRS** : 0.83 (95% CI: 0.71 to 0.91) | **Pooled specificity SIRS** : 0.49 (95% CI: 0.29 to 0.69)  
Bibliography: Song JU, Sin CK, Park HK, Shim SR, Lee J. Performance of the quick Sequential (sepsis-related) Organ Failure Assessment score as a prognostic tool in infected patients outside the intensive care unit: a systematic review and meta-analysis. Crit Care. 2018 Feb 6;22(1):28. doi: 10.1186/s13054-018-1952-x.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Test result** | **Number of results per 1,000 patients tested (95% CI)** | | | | **Number of participants  (studies)** | **Quality of the Evidence (GRADE)** |
| **Prevalence 10%**  Typically seen in | | **Prevalence 50%**  Typically seen in | |
| qSOFA | SIRS | qSOFA | SIRS |
| **True positives** | **47** (28 to 66) | **83** (71 to 91) | **235** (140 to 330) | **415** (355 to 455) | 15669 (9) | ⨁⨁◯◯ **LOW** a,b |
| **36 fewer TP in qSOFA** | | **180 fewer TP in qSOFA** | |
| **False negatives** | **53** (34 to 72) | **17** (9 to 29) | **265** (170 to 360) | **85** (45 to 145) |
| **36 more FN in qSOFA** | | **180 more FN in qSOFA** | |
| **True negatives** | **837** (792 to 873) | **441** (261 to 621) | **465** (440 to 485) | **245** (145 to 345) | 15669 (9) | ⨁⨁◯◯ **LOW** a,b |
| **396 more TN in qSOFA** | | **220 more TN in qSOFA** | |
| **False positives** | **63** (27 to 108) | **459** (279 to 639) | **35** (15 to 60) | **255** (155 to 355) |
| **396 fewer FP in qSOFA** | | **220 fewer FP in qSOFA** | |

**CI:** Confidence interval

#### Explanations

a. 5 out of 9 studies judged at high risk of bias.

b. We downgraded for inconsistency by 1 point as significant heterogeneity detected (i2 = 99%).

## Evidence profile: qSOFA versus MEWS to screen for sepsis

**Setting** : critically ill patients

**Pooled sensitivity qSOFA** : 0.47 (95% CI: 0.28 to 0.66) | **Pooled specificity qSOFA** : 0.93 (95% CI: 0.88 to 0.97)

**Pooled sensitivity MEWS** : 0.80 (95% CI: 0.79 to 0.81) | **Pooled specificity MEWS** : 0.73 (95% CI: 0.73 to 0.73)

**Bibliography:** Islam MM, Nasrin T, Walther BA, Wu CC, Yang HC, Li YC. Prediction of sepsis patients using machine learning approach: A meta-analysis. Comput Methods Programs Biomed. 2019 Mar;170:1-9. doi: 10.1016/j.cmpb.2018.12.027.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Test result** | **Number of results per 1,000 patients tested (95% CI)** | | | | **Number of participants  (studies)** | **Quality of the Evidence (GRADE)** |
| **Prevalence 10%**  Typically seen in | | **Prevalence 50%**  Typically seen in | |
| qSOFA | MEWS | qSOFA | MEWS |
| **True positives** | **47** (28 to 66) | **80** (79 to 81) | **235** (140 to 330) | **400** (395 to 405) | (0) | - |
| **33 fewer TP in qSOFA** | | **165 fewer TP in qSOFA** | |
| **False negatives** | **53** (34 to 72) | **20** (19 to 21) | **265** (170 to 360) | **100** (95 to 105) |
| **33 more FN in qSOFA** | | **165 more FN in qSOFA** | |
| **True negatives** | **837** (792 to 873) | **657** (657 to 657) | **465** (440 to 485) | **365** (365 to 365) | (0) | - |
| **180 more TN in qSOFA** | | **100 more TN in qSOFA** | |
| **False positives** | **63** (27 to 108) | **243** (243 to 243) | **35** (15 to 60) | **135** (135 to 135) |
| **180 fewer FP in qSOFA** | | **100 fewer FP in qSOFA** | |

**CI:** Confidence interval

## 

## Evidence profile: qSOFA versus SOFA to screen for sepsis

**Setting** : critically ill patients

**Pooled sensitivity qSOFA** : 0.47 (95% CI: 0.28 to 0.66) | **Pooled specificity qSOFA** : 0.93 (95% CI: 0.88 to 0.97)

**Pooled sensitivity SOFA** : 0.77 (95% CI: 0.76 to 0.78) | **Pooled specificity SOFA** : 0.42 (95% CI: 0.42 to 0.42)

**Bibliography:** Islam MM, Nasrin T, Walther BA, Wu CC, Yang HC, Li YC. Prediction of sepsis patients using machine learning approach: A meta-analysis. Comput Methods Programs Biomed. 2019 Mar;170:1-9. doi: 10.1016/j.cmpb.2018.12.027.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Test result** | **Number of results per 1,000 patients tested (95% CI)** | | | | **Number of participants  (studies)** | **Quality of the Evidence (GRADE)** |
| **Prevalence 10%**  Typically seen in | | **Prevalence 50%**  Typically seen in | |
| qSOFA | SOFA | qSOFA | SOFA |
| **True positives** | **47** (28 to 66) | **77** (76 to 78) | **235** (140 to 330) | **385** (380 to 390) | (0) | - |
| **30 fewer TP in qSOFA** | | **150 fewer TP in qSOFA** | |
| **False negatives** | **53** (34 to 72) | **23** (22 to 24) | **265** (170 to 360) | **115** (110 to 120) |
| **30 more FN in qSOFA** | | **150 more FN in qSOFA** | |
| **True negatives** | **837** (792 to 873) | **378** (378 to 378) | **465** (440 to 485) | **210** (210 to 210) | (0) | - |
| **459 more TN in qSOFA** | | **255 more TN in qSOFA** | |
| **False positives** | **63** (27 to 108) | **522** (522 to 522) | **35** (15 to 60) | **290** (290 to 290) |
| **459 fewer FP in qSOFA** | | **255 fewer FP in qSOFA** | |

**CI:** Confidence interval

## 

## **EtD:** Summary of judgements for the standardized screening process recommendation

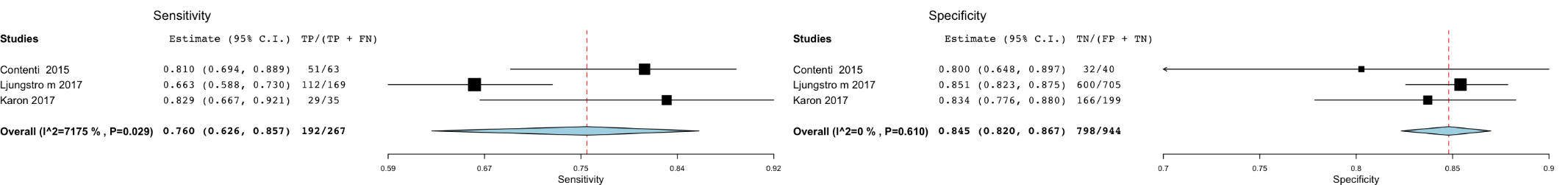
|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | Yes |  | Varies | Don't know |
| **Test accuracy** | Very inaccurate | **Inaccurate** | Accurate | Very accurate |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | **Moderate** | Small | Trivial |  | Varies | Don't know |
| **Certainty of the evidence of test accuracy** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Certainty of the evidence of test's effects** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Certainty of the evidence of management's effects** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Certainty of the evidence of test result/management** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Certainty of effects** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | **Probably no** | Probably yes | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

## Type of Recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Strong recommendation against the intervention** | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| **●** | ○ | ○ | ○ | ○ |

# In patients with suspected sepsis or septic shock should we use serum lactate to screen for sepsis?

## Forest plot for sensitivity and specificity



## 

## Evidence profile: serum lactate to screen for sepsis

**Setting** : critically ill patients

**Pooled sensitivity** : 0.76 (95% CI: 0.64 to 0.84) | **Pooled specificity** : 0.84 (95% CI: 0.80 to 0.87)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Test result** | **Number of results per 1,000 patients tested (95% CI)** | | **Number of participants  (studies)** | **Quality of the Evidence (GRADE)** |
| **Prevalence 10%**  Typically seen in | **Prevalence 50%**  Typically seen in |
| **True positives** | **76** (64 to 84) | **380** (320 to 420) | 1211 (3) | ⨁⨁⨁⨁ **HIGH** |
| **False negatives** | **24** (16 to 36) | **120** (80 to 180) |
| **True negatives** | **756** (720 to 783) | **420** (400 to 435) | 1211 (3) | - |
| **False positives** | **144** (117 to 180) | **80** (65 to 100) |

**CI:** Confidence interval

## 

## **EtD:** Summary of judgements for the lactate to screen for sepsis recommendation

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Test accuracy** | Very inaccurate | Inaccurate | **Accurate** | Very accurate |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | Moderate | **Large** |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |
| **Certainty of the evidence of test accuracy** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Certainty of the evidence of test's effects** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Certainty of the evidence of management's effects** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Certainty of the evidence of test result/management** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Certainty of effects** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |

## 

## **Type of Recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# 

# In patients with known or suspected infection and hypotension and / or an elevated lactate should we administer 30mL/Kg BW of crystalloids or a rapid small volume fluid challenge and re-assess?

## **EtD:** Summary of judgements for the 30 ml/kg BW recommendation

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | Moderate | Large |  | **Varies** | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | **Varies** | Don't know |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

## 

## **Type of Recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# 

# In hypotensive patients with known or suspected sepsis or septic shock should dynamic response (SV, SVV, PPV, echo) to fluid boluses or straight leg raise guide initial fluid resuscitation?

## Evidence profile: dynamic response (SV, SVV, PPV, echo) to fluid boluses or straight leg raise compared to control

**Setting**: critically ill patients

**Bibliography**: Ehrman RR, Gallien JZ, Smith RK, et al. Resuscitation Guided by Volume Responsiveness Does Not Reduce Mortality in Sepsis: A Meta-Analysis. Crit Care Explor. 2019;1(5):e0015. Published 2019 May 23. doi:10.1097/CCE.0000000000000015

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **dynamic response (SV, SVV, PPV, echo) to fluid boluses or straight leg raise** | **control** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality (assessed with: shot term (ICU, hospital 28 days))** | | | | | | | | | | | | |
| 4 | randomised trials | not serious | not serious | not serious | serious a | none | 56/185 (30.3%) | 59/180 (32.8%) | **RR 0.87** (0.49 to 1.54) | **43 fewer per 1,000** (from 167 fewer to 177 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Need for RRT** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious b | none | 32/94 (34.0%) | 37/89 (41.6%) | **RR 0.83** (0.51 to 1.35) | **71 fewer per 1,000** (from 204 fewer to 146 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Intravascular volume expansion H0-H72 (L) (assessed with: Litres)** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious c | very serious b | none | 66 | 68 | - | MD **0.13 L higher** (0.94 lower to 1.2 higher) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Number of days with organ system failure (that is SOFA ≥6)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious c | very serious b | none | 30 | 30 | - | MD **0**  (1.67 lower to 1.67 higher) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Pulmonary edema (assessed with: Number of days with pulmonary edema (that is ELWI >10 ml.kg-1 PBW))** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious c | very serious b | none | 30 | 30 | - | MD **0**  (1.7 lower to 1.7 higher) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Adverse events - Pulmonary edema** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious c | very serious b | none | 4/58 (6.9%) | 4/64 (6.3%) | **RR 1.10** (0.29 to 4.21) | **6 more per 1,000** (from 44 fewer to 201 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Time to shock resolution (days)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious c | very serious b | none | 30 | 30 | - | MD **0.3 lower** (1.52 lower to 0.92 higher) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Ventilator-free days** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious c | very serious b | none | 71 | 71 | - | MD **1.93 lower** (7.41 lower to 3.56 higher) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **AKI** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious c | serious d | none | 39/111 (35.1%) | 47/112 (42.0%) | **RR 0.82** (0.50 to 1.36) | **76 fewer per 1,000** (from 210 fewer to 151 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Ventilator days** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious c | very serious b | none | 41 | 41 | - | MD **3 higher** (0.04 lower to 6.04 higher) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **ICU LOS (assessed with: days)** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious b | none | 83 | 78 | - | MD **0.6 lower** (2.21 lower to 1.01 higher) | ⨁⨁◯◯ LOW | CRITICAL |
| **Adverse events - Central line complications** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | not serious | none | 0/58 (0.0%) | 0/64 (0.0%) | not estimable |  | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **Adverse events - Nosocomial infection** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious b | none | 2/58 (3.4%) | 1/64 (1.6%) | **RR 2.21** (0.21 to 23.70) | **19 more per 1,000** (from 12 fewer to 355 more) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. We downgraded for imprecision by 2 points: small number of events (117) and confidence interval includes both significant benefit and harm.

b. We downgraded by 2 points for imprecision due to small sample size and confidence interval including significant benefit and harm.

c. Not a patient important outcome.

d. We downgraded by one point for imprecision due to small sample and events size.

## 

## **EtD:** Summary of judgements for the dynamic response (SV, SVV, PPV, echo) to fluid boluses or straight leg raise

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | Yes |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | **Varies** | Don't know |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |
| **Feasibility** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |

## **Type of Recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# 

# In patients with suspected sepsis or septic shock, should fluid resuscitation be guided by physical examination, static or dynamic parameters?

## Evidence profile: physical examination, static or dynamic parameters to guide fluid resuscitation

**Setting**: critically ill patients

**Bibliography**: Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA. 2019;321(7):654–664. doi:10.1001/jama.2019.0071

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **fluid resuscitation be guided by physical examination,** | **static or dynamic parameters** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality - CRT** | | | | | | | | | | | | |
| 1 | randomised trials | serious | not serious | not serious | serious | none | 92/212 (43.4%) | 74/212 (34.9%) | **HR 0.75** (0.55 to 1.02) | **74 fewer per 1,000** (from 139 fewer to 6 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Mortality - Temperature** | | | | | | | | | | | | |
| 2 | observational studies | not serious | not serious | not serious | not serious | none | -/0 | 10.0% | **OR 1.27** (0.97 to 1.67) | **24 more per 1,000** (from 3 fewer to 57 more) | ⨁⨁◯◯ LOW | CRITICAL |
| 30.0% | **52 more per 1,000** (from 6 fewer to 117 more) |
| **Mortality - Any Skin Mottling** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | serious | none | -/0 | 10.0% | **OR 3.29** (2.08 to 5.19) | **168 more per 1,000** (from 88 more to 266 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| 30.0% | **285 more per 1,000** (from 171 more to 390 more) |
| **Mortality - Skin Mottling - SMS 2-3** | | | | | | | | | | | | |
| 2 | observational studies | not serious | not serious | not serious | serious | none | -/0 | 10.0% | **OR 8.52** (2.20 to 32.96) | **386 more per 1,000** (from 96 more to 686 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| 30.0% | **485 more per 1,000** (from 185 more to 634 more) |
| **Mortality - Skin Mottling - SMS 4-5** | | | | | | | | | | | | |
| 2 | observational studies | not serious | not serious | not serious | serious | none | -/0 | 10.0% | **OR 47.76** (10.76 to 211.96) | **741 more per 1,000** (from 445 more to 859 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| 30.0% | **653 more per 1,000** (from 522 more to 689 more) |

**CI:** Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

## 

## **EtD:** Summary of judgements for the dynamic response (SV, SVV, PPV, echo) to fluid boluses or straight leg raise

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | Yes |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | **Moderate savings** | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

## Type of Recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# 

# In patients with sepsis and increased serum lactate, should lactate decrease be considered a target of initial sepsis resuscitation?

## Evidence profile: lactate decrease as target for initial resuscitation

**Setting**: critically ill patients

**Bibliography**:

1. Gu WJ, Zhang Z, Bakker J. Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. Intensive Care Med. 2015 Oct;41(10):1862-3. doi: 10.1007/s00134-015-3955-2. Epub 2015 Jul 8.
2. Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA. 2019;321(7):654–664. doi:10.1001/jama.2019.0071

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **lactate clearance** | **No specific intervention for lactate** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality - subgroup analysis (assessed with: short term)** | | | | | | | | | | | | |
| 8 | randomised trials | not serious | serious a | serious b | not serious | none | 254/857 (29.6%) | 299/844 (35.4%) | **RR 0.75** (0.59 to 0.96) | **89 fewer per 1,000** (from 145 fewer to 14 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| **Mortality - subgroup analysis - LC Vs EGDT (assessed with: short term)** | | | | | | | | | | | | |
| 7 | randomised trials | not serious | not serious | serious b | not serious | none | 162/645 (25.1%) | 225/632 (35.6%) | **RR 0.70** (0.59 to 0.82) | **107 fewer per 1,000** (from 146 fewer to 64 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Mortality - subgroup analysis - Capillary refil q 30 mins (assessed with: short term)** | | | | | | | | | | | | |
| 1 | randomised trials | serious c | not serious | serious b | serious d | none | 92/212 (43.4%) | 74/212 (34.9%) | **RR 1.24** (0.98 to 1.58) | **84 more per 1,000** (from 7 fewer to 202 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Need for renal replacement therapy (assessed with: ANDROMEDA trial)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious e | none | -/177 | 10.0% | **HR 0.56** (0.22 to 1.43) | **43 fewer per 1,000** (from 77 fewer to 40 more) | ⨁⨁◯◯ LOW | CRITICAL |
| 20.0% | **83 fewer per 1,000** (from 152 fewer to 73 more) |
| **RRT -RCT** | | | | | | | | | | | | |
| 1 | randomised trials | serious c | not serious | serious b | serious d | none | 42/212 (19.8%) | 30/212 (14.2%) | **RR 1.40** (0.91 to 2.15) | **57 more per 1,000** (from 13 fewer to 163 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **RBC transfusion** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious f | none | 15/175 (8.6%) | 10/75 (13.3%) | **RR 0.76** (0.35 to 1.64) | **32 fewer per 1,000** (from 87 fewer to 85 more) | ⨁⨁◯◯ LOW |  |
| **Total fluids in first day 0-8 hours** | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | serious g | serious h | none | 501 | 507 | - | MD **0.4 higher** (0.09 higher to 0.7 higher) | ⨁⨁◯◯ LOW |  |
| **Total fluids in first day 9-72 hours** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | serious i | serious g | very serious j | none | 321 | 327 | - | MD **0.5 lower** (2.59 lower to 1.58 higher) | ⨁◯◯◯ VERY LOW |  |
| **Mechanical Ventilation** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious f | none | 60/175 (34.3%) | 58/175 (33.1%) | **RR 1.04** (0.83 to 1.32) | **13 more per 1,000** (from 56 fewer to 106 more) | ⨁⨁◯◯ LOW |  |
| **Vasopressors infusion** | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | serious g | serious k | none | 245/346 (70.8%) | 246/352 (69.9%) | **RR 1.00** (0.91 to 1.11) | **0 fewer per 1,000** (from 63 fewer to 77 more) | ⨁⨁◯◯ LOW |  |
| **Dobutamine use** | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | serious g | very serious f | none | 76/346 (22.0%) | 67/352 (19.0%) | **RR 1.19** (0.91 to 1.56) | **36 more per 1,000** (from 17 fewer to 107 more) | ⨁◯◯◯ VERY LOW |  |
| **Adverse events - Acute pulmonary edema** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious f | none | 1/180 (0.6%) | 1/180 (0.6%) | **RR 1.00** (0.06 to 15.86) | **0 fewer per 1,000** (from 5 fewer to 83 more) | ⨁⨁◯◯ LOW |  |
| **Adverse events - Acute MI** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious f | none | 0/180 (0.0%) | 1/180 (0.6%) | **RR 0.33** (0.01 to 8.13) | **4 fewer per 1,000** (from 6 fewer to 40 more) | ⨁⨁◯◯ LOW |  |
| **Adverse events - Arryhtmia** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious f | none | 2/180 (1.1%) | 3/180 (1.7%) | **RR 0.67** (0.11 to 3.94) | **6 fewer per 1,000** (from 15 fewer to 49 more) | ⨁⨁◯◯ LOW |  |
| **Adverse events - Cardiac arrest** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious f | none | 0/180 (0.0%) | 0/180 (0.0%) | not estimable |  | ⨁⨁◯◯ LOW |  |
| **Adverse events - Pneumothorax caused by the puncture** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious f | none | 0/180 (0.0%) | 0/180 (0.0%) | not estimable |  | ⨁⨁◯◯ LOW |  |
| **Adverse events - RBC allergy** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious f | none | 0/180 (0.0%) | 0/180 (0.0%) | not estimable |  | ⨁⨁◯◯ LOW |  |
| **Adverse events - Catheter related infections** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious f | none | 1/180 (0.6%) | 0/180 (0.0%) | **RR 3.00** (0.12 to 73.16) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁⨁◯◯ LOW |  |

**CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **MD:** Mean difference

#### Explanations

a. We downgraded by 1 point for inconsistency as significant heterogeneity detected (i2=62%)

b. Our intervention was lactate normalization where the studies included where about lactate clearance.

c. Control arm required patients to be assessed every 30 minutes which can lead to co-interventions compared to lactate clearance group which lactate was assessed every 2 hours.

d. We downgraded for imprecision by 1 point as confidence interval included both significant benefits and harms.

e. We downgraded for imprecision by 2 points as CI includes both significant benefit and very wide confidence interval.

f. We downgraded for imprecision by 2 points as CI includes both significant benefit and harm as well as number of events <300.

g. Not a patient-important outcome.

h. We downgraded by 1 point for imprecision as confidence interval is very wide (10 ml to 700 mls).

i. We downgraded by 1 point for inconsistency as significant heterogeneity detected (i2 = 80%).

j. We downgraded by 2 points for imprecision as confidence interval is very wide (2.59 litres less to 1.6 litre more) and crossed unity.

k. We downgraded for imprecision as CI crossed unity line.

## 

## **EtD:** Summary of judgements for lactate decrease as a target of initial sepsis resuscitation

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | **Favors the intervention** | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

## **Type of Recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# In patients with known or suspected sepsis or septic shock should we target a mean arterial pressure of ≥ 65 mm Hg?

## Evidence profile: targeting MAP ≥65 mmHg

**Setting**: critically ill patients

**Bibliography**: Hylands M, Moller MH, Asfar P, Toma A, Frenette AJ, Beaudoin N, Belley-Côté É, D'Aragon F, Laake JH, Siemieniuk RA, Charbonney E, Lauzier F, Kwong J, Rochwerg B, Vandvik PO, Guyatt G, Lamontagne F. A systematic review of vasopressor blood pressure targets in critically ill adults with hypotension. Can J Anaesth. 2017 Jul;64(7):703-715.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **we target a mean arterial pressure of ≥ 65 mm Hg** | **higher targets** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Short term mortality** | | | | | | | | | | | | |
| 2 | randomised trials | not serious b | not serious | not serious | serious c | none | 148/448 (33.0%) | 161/446 (36.1%) | **RR 0.92** (0.76 to 1.10) | **29 fewer per 1,000** (from 87 fewer to 36 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Long-term mortality** | | | | | | | | | | | | |
| 2 | randomised trials | not serious b | not serious | not serious | serious d | none | 184/448 (41.1%) | 193/446 (43.3%) | **RR 0.95** (0.82 to 1.11) | **22 fewer per 1,000** (from 78 fewer to 48 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Renal replacement therapy** | | | | | | | | | | | | |
| 2 | randomised trials | not serious b | not serious | not serious | serious e | none | -/448 | -/446 | **RR 0.96** (0.80 to 1.14) | **14 fewer per 1,000** (from 71 fewer to 50 more) f | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Renal Replacement Therapy - subgroup with chronic hypertension** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | serious g | none | 73/173 (42.2%) | 53/167 (31.7%) | **RR 1.33** (1.00 to 1.76) | **105 more per 1,000** (from 0 fewer to 241 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Time on vasopressors** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious h | not serious | none | 388 | 388 | - | MD **1 lower** (1.49 lower to 0.51 lower) | ⨁⨁⨁◯ MODERATE | IMPORTANT |
| **Digit ischemia** | | | | | | | | | | | | |
| 2 | randomised trials | not serious b | not serious | not serious | very serious i | none | 12/447 (2.7%) | 11/446 (2.5%) | **RR 1.06** (0.46 to 2.42) | **1 more per 1,000** (from 13 fewer to 35 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Ventricular arrythmias** | | | | | | | | | | | | |
| 2 | randomised trials | not serious b | not serious | not serious | very serious j | none | 18/447 (4.0%) | 26/446 (5.8%) | **RR 0.69** (0.38 to 1.24) | **18 fewer per 1,000** (from 36 fewer to 14 more) | ⨁⨁◯◯ LOW | IMPORTANT |
| **Myocardial ischemia** | | | | | | | | | | | | |
| 2 | randomised trials | not serious b | not serious | not serious | very serious k | none | 13/447 (2.9%) | 16/446 (3.6%) | **RR 0.69** (0.38 to 2.72) | **11 fewer per 1,000** (from 22 fewer to 62 more) | ⨁⨁◯◯ LOW | IMPORTANT |
| **Bowel ischemia** | | | | | | | | | | | | |
| 2 | randomised trials | not serious b | not serious | not serious | very serious l | none | 13/447 (2.9%) | 11/446 (2.5%) | **RR 1.17** (0.53 to 2.60) | **4 more per 1,000** (from 12 fewer to 39 more) | ⨁⨁◯◯ LOW | IMPORTANT |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. We downgraded for imprecision by 2 points as 95% confidence interval included significant benefit and harm (0.45, 2.48) and number of events < 300.

b. We did not consider lack of blinding as a risk of bias as the intervention cannot be blinded.

c. We downgraded for imprecision by 2 points as 95% confidence interval included significant benefit and harm (0.77, 1.12) and number of events < 300.

d. We downgraded for imprecision by 1 point as 95% confidence interval included significant benefit and harm (0.82, 1.11).

e. We downgraded for imprecision by 1 point as 95% confidence interval included significant benefit and harm (0.8, 1.14)

f. Pooled data from meta-analysis and could not obtain from primary studies.

g. We downgraded for imprecision by 1 point as confidence interval included significant benefits and harms as well as total number of events < 300.

h. We downgraded for indirectness by 1 point as time on vasopressors is not a patient important outcome.

i. We downgraded for imprecision by 2 points as 95% confidence interval included significant benefit and harm (0.45, 2.48) and number of events < 300.

j. We downgraded for imprecision by 2 points as 95% confidence interval included significant benefit and harm (0.38, 1.24) and number of events < 300.

k. We downgraded for imprecision by 2 points as 95% confidence interval included significant benefit and harm (0.38, 1.24) and number of events < 300.

l. We downgraded for imprecision by 2 points as 95% confidence interval included significant benefit and harm (0.53, 2.6) and number of events < 300.

## 

## **EtD:** Summary of judgements for targeting MAP ≥65 mmHg

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | Yes |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | **Varies** | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

## **Type of Recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | **Strong recommendation for the intervention** |
| ○ | ○ | ○ | ○ | **●** |

# In patients with known or suspected sepsis or septic shock, should we admit to ICU in less than 6 hours?

## Evidence profile: admission to ICU in < 6 hours

**Setting**: critically ill patients

**Bibliography**: Groenland Emergency Department to ICU Time Is Associated With Hospital Mortality: A Registry Analysis of 14,788 Patients From Six University Hospitals in the Netherlands. Crit Care Med. 2019 Nov;47(11):1564-1571. doi: 10.1097/CCM.0000000000003957.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **we admit to ICU in ≤ 6 hours** | **>6 hours** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Hospital mortality** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | serious a | not serious | none |  | 10.0% | **OR 1.27** (1.08 to 1.49) | **24 more per 1,000** (from 7 more to 42 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| 40.0% | **58 more per 1,000** (from 19 more to 98 more) |
| **ICU mortality** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | serious a | serious b | none |  | 10.0% | **OR 1.14** (0.96 to 1.37) | **12 more per 1,000** (from 4 fewer to 32 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| 40.0% | **32 more per 1,000** (from 10 fewer to 77 more) |
| **30-d Mortality** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | serious a | not serious | none |  | 10.0% | **HR 1.18** (1.05 to 1.33) | **17 more per 1,000** (from 5 more to 31 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| 40.0% | **53 more per 1,000** (from 15 more to 93 more) |
| **90-d Mortality** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | serious a | not serious | none |  | 10.0% | **HR 1.23** (1.11 to 1.37) | **22 more per 1,000** (from 10 more to 34 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| 40.0% | **67 more per 1,000** (from 33 more to 103 more) |
| **Mortality < 6 hours vs > 6 hours** | | | | | | | | | | | | |
| 3 | observational studies | not serious | not serious | not serious a | not serious | none |  | 10.0% | **OR 1.32** (1.10 to 1.59) | **28 more per 1,000** (from 9 more to 50 more) | ⨁⨁◯◯ LOW | CRITICAL |
| 40.0% | **68 more per 1,000** (from 23 more to 115 more) |

**CI:** Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio

#### Explanations

a. We downgraded for indirectness by 1 points as population is not only sepsis patients

b. We downgraded for imprecision by 1 point

## **EtD:** Summary of judgements for admission to ICU in < 6 hours

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |
| **Feasibility** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |

## **Type of Recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |