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# In adult critically ill patients, how accurate is oral temperature compared to core temperature measured by pulmonary artery, esophageal or bladder?

## Oral temperature: Evidence profile:

**Setting**: ICU

**Bibliography**: Niven DJ, Gaudet JE, Laupland KB, Mrklas KJ, Roberts DJ, Stelfox HT. Accuracy of peripheral thermometers for estimating temperature: a systematic review and meta-analysis. Ann Intern Med. 2015 Nov 17;163(10):768-77. doi: 10.7326/M15-1150. PMID: 26571241.(1)

| **Certainty assessment** | | | | | | | **Impact** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| 7 | observational studies | not serious | serious a | serious b | serious c | none | LOA Oral and central thermometers in adults: Pooled mean difference -0.06 (95% -76 to 0.63)  Therefore, on average, oral temperatures are 0.06 degrees lower than core temperature, but could be 0.76 lower to 0.63 higher. | ⨁◯◯◯ VERY LOW | CRITICAL |

#### CI: Confidence interval

#### Explanations

a. We downgraded for Inconsistency by 1 point as significant heterogeneity was detected I2=99.1%

b. We downgraded for indirectness by 1 point as many studies were on peri-operative population.

c. We downgraded for imprecision by 1 point as consequences at lower and higher ends of CI can vary significantly.

## Graphical user interface, website Description automatically generatedEtD: Summary of judgements for oral temperature recommendation

## Type of recommendation

# In adult critically ill patients, how accurate is rectal temperature compared to core temperature measured by pulmonary artery, esophageal or bladder?

## Rectal temperature: Evidence profile:

**Setting**: ICU

**Bibliography**: Niven DJ, Gaudet JE, Laupland KB, Mrklas KJ, Roberts DJ, Stelfox HT. Accuracy of peripheral thermometers for estimating temperature: a systematic review and meta-analysis. Ann Intern Med. 2015 Nov 17;163(10):768-77. doi: 10.7326/M15-1150. PMID: 26571241.(1)

| **Certainty assessment** | | | | | | | **Impact** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| 4 | observational studies | not serious | not serious | serious a | not serious | none | Mean Difference between rectal and pulmonary artery catheter temperature C −0.10 (−0.17 to −0.03).  On average, rectal temperature is 0.1 C lower than PAC temperature but could be 0.17 to 0.03 lower. | ⨁◯◯◯ VERY LOW |  |

#### Explanations

a. We downgraded for indirectness by 1 point as many studies were on perioperative and not restricted to adults population.

## Graphical user interface, website, timeline Description automatically generatedEtD: Summary of judgements for rectal temperature recommendation

## Type of recommendation

# In adult critically ill patients, how accurate is axillary temperature compared to core temperature measured by pulmonary artery, esophageal or bladder?

## Axillary temperature: Evidence profile:

**Setting**: ICU

**Bibliography**: Niven DJ, Gaudet JE, Laupland KB, Mrklas KJ, Roberts DJ, Stelfox HT. Accuracy of peripheral thermometers for estimating temperature: a systematic review and meta-analysis. Ann Intern Med. 2015 Nov 17;163(10):768-77. doi: 10.7326/M15-1150. PMID: 26571241.(1)

| **Certainty assessment** | | | | | | | **Impact** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| 13 | observational studies | not serious | serious a | serious b | serious c | none | LOA Axillary and central thermometers in adults: Pooled mean difference −0.33 (−0.94 to 0.27)  Therefore, on average, axillary temperatures are 0.33 degrees lower than core temperature, but could be 0.94 lower to 0.27 higher. | ⨁◯◯◯ VERY LOW | CRITICAL |

#### Explanations

a. We downgraded for Inconsistency by 1 point as significant heterogeneity was detected I2=98.7%

b. We downgraded for indirectness by 1 point as many studies were on perioperative population.

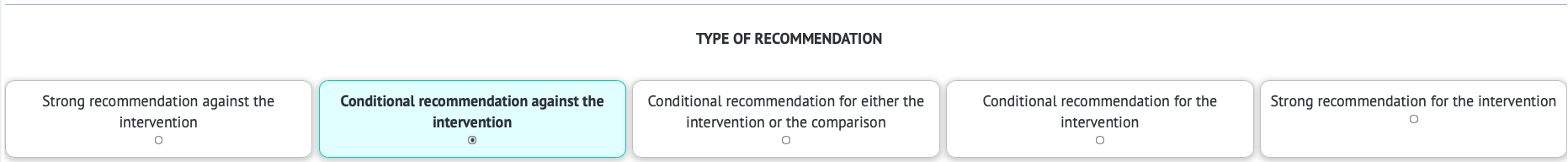
c. We downgraded for imprecision by 1 point as consequences at different lower and higher end of CI can vary significantly.

## EtD: Summary of judgements for axillary temperature recommendation

Graphical user interface, website

Description automatically generated

## Type of recommendation



# In adult critically ill patients, how accurate is tympanic temperature compared to core temperature measured by pulmonary artery, esophageal or bladder?

## Tympanic temperature: Evidence profile:

**Setting**: ICU

**Bibliography**:

Niven DJ, Gaudet JE, Laupland KB, Mrklas KJ, Roberts DJ, Stelfox HT. Accuracy of peripheral thermometers for estimating temperature: a systematic review and meta-analysis. Ann Intern Med. 2015 Nov 17;163(10):768-77. doi: 10.7326/M15-1150. PMID: 26571241. (1)

Poveda VB, Nascimento AS. Intraoperative body temperature control: esophageal thermometer versus infrared tympanic thermometer. Rev Esc Enferm USP. 2016 Nov-Dec;50(6):946-952. English, Portuguese. doi: 10.1590/S0080-623420160000700010. PMID: 28198959.(2)

| **Certainty assessment** | | | | | | | **Impact** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| 22 | observational studies | not serious | serious a | serious b | serious c | none | Niven 2015: LOA Tympanic and central thermometers in adults: Pooled mean difference -0.08 (95% -1.42 to 1.26).(1)  Poveda 2016: 1 study identified after the Niven meta-analysis above found tympanic measurements were consistently 1.24°C lower (p<0.0001) than esophageal.(2) | ⨁◯◯◯ VERY LOW | CRITICAL |

#### Explanations

a. We downgraded for Inconsistency by 1 point as significant heterogeneity was detected I2=98.8%.

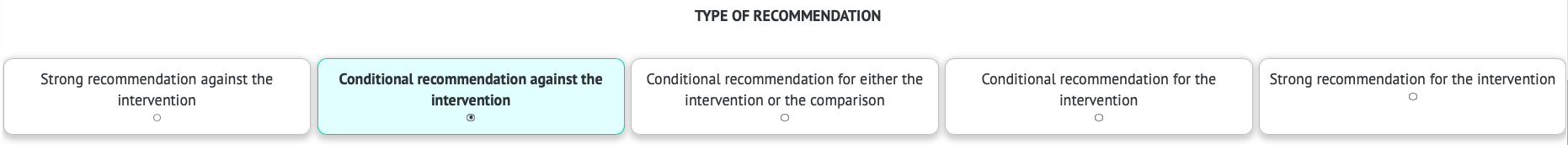
b. We downgraded for indirectness by 1 point as many studies were on perioperative population.

c. We downgraded for imprecision by 1 point as the upper and lower limits of 95% confidence interval lead to very different actions (1.42 lower to 1.26 higher).

## EtD: Summary of judgements for tympanic temperature recommendation

Graphical user interface, website

Description automatically generated



## Type of recommendation

# In adult critically ill patients, how accurate is temporal temperature compared to core temperature measured by pulmonary artery, esophageal or bladder?

## Temporal temperature: Evidence profile:

**Setting**: ICU

**Bibliography**:

Niven DJ, Gaudet JE, Laupland KB, Mrklas KJ, Roberts DJ, Stelfox HT. Accuracy of peripheral thermometers for estimating temperature: a systematic review and meta-analysis. Ann Intern Med. 2015 Nov 17;163(10):768-77. doi: 10.7326/M15-1150. PMID: 26571241. (1)

Furlong D, Carroll DL, Finn C, Gay D, Gryglik C, Donahue V. Comparison of temporal to pulmonary artery temperature in febrile patients. Dimens Crit Care Nurs. 2015 Jan-Feb;34(1):47-52. doi: 10.1097/DCC.0000000000000090. PMID: 25470268. (3)

| **Certainty assessment** | | | | | | | **Impact** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| 5 | observational studies | not serious | serious a | serious b | serious c | none | Niven 2015: LOA Temporal and central thermometers in adults: Pooled mean difference 0.09 (−0.64 to 0.82).(1)  Furlong 2015: in patients with temperature ≥38C, temporal artery temperature was on average 0.9 C lower than pulmonary artery temperature with 25% vaariability.(3)  Therefore, on average, axillary temperatures are 0.09 degrees higher than core temperature, but could be 0.64 lower to 0.82 higher. | ⨁◯◯◯ VERY LOW | CRITICAL |

#### Explanations

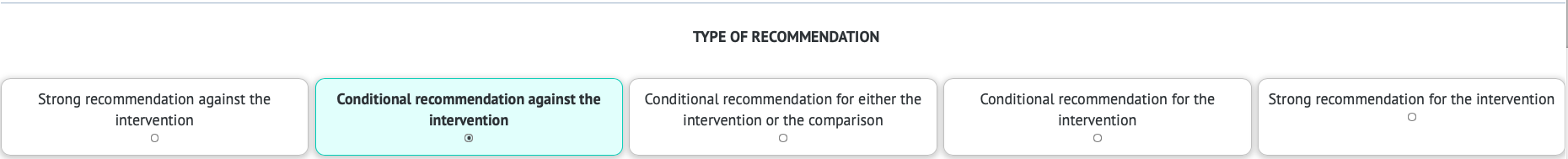
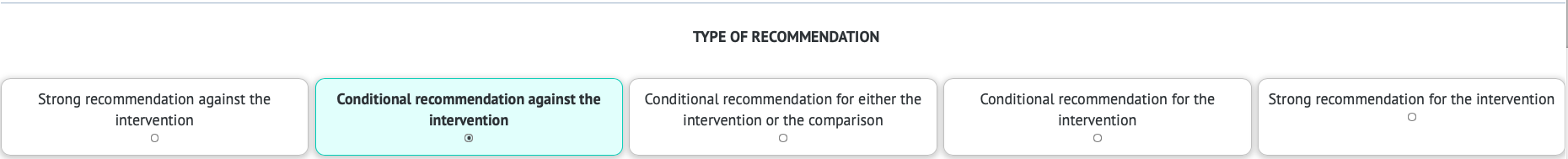
a. We downgraded for Inconsistency by 1 point as significant heterogeneity was detected I2=99%.

b. We downgraded for indirectness by 1 point as many studies were on perioperative population.

c. We downgraded for imprecision by 1 point as consequences at lower and higher ends of CI can vary significantly.

## Timeline Description automatically generatedEtD: Summary of judgements for temporal temperature recommendation

## Type of recommendation



## Summary table for different temperature measurement methods



# In adult critically ill patients with fever, is there benefit with lowering the body temperature?

## Evidence profile

**Setting**: ICU   
**Bibliography**: Sakkat A, Alquraini M, Aljazeeri J, Farooqi MAM, Alshamsi F, Alhazzani W. Temperature control in critically ill patients with fever: A meta-analysis of randomized controlled trials. J Crit Care. 2021;61:89-95. doi:10.1016/j.jcrc.2020.10.016 (4)

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Fever Managment** | **No intervention** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Survival at 90 days (IPDMA) (follow up: 90 days)1** | | | | | | | | | | | | |
| 5 | randomised trials | not serious | not serious | not serious | serious a | none |  | 80.0% | **HR 0.91** (0.75 to 1.10) | **31 fewer per 1,000** (from 99 fewer to 30 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **ICU Mortality** | | | | | | | | | | | | |
| 11 | randomised trials | not serious | not serious | not serious | serious a | none | 220/877 (25.1%) | 222/868 (25.6%) | **RR 1.03** (0.79 to 1.35) | **8 more per 1,000** (from 54 fewer to 90 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Hospital Mortality** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious b | none | 56/364 (15.4%) | 61/366 (16.7%) | **OR 0.84** (0.40 to 1.77) | **23 fewer per 1,000** (from 93 fewer to 95 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Temperature Level** | | | | | | | | | | | | |
| 7 | randomised trials | not serious | not serious c | not serious | serious d | none | 484 | 477 | - | MD **0.45 °C lower** (0.8 lower to 0.09 lower) | ⨁⨁⨁◯ MODERATE | IMPORTANT |

#### HR: Hazard Ratio; RR: Risk ratio; OR: Odds ratio; MD: Mean difference Explanations

a. We downgraded the quality of evidence by one level for serious imprecision; the CI included large benefit and harm

b. We downgraded the quality of evidence by two levels for very serious imprecision; the CI included both substantial benefit and harm

c. Although the I2>90% we did not downgrade the quality of evidence for inconsistency, the variation between point estimates was small clinically, we opted not downgrade

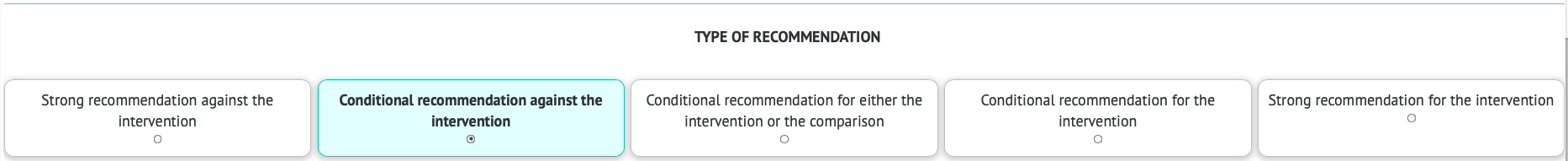
d. We downgraded the quality of evidence by one level for imprecision; the CI included a negligible benefit (-0.09 °C) which is not clinically relevant

e. We downgraded the quality of evidence by one level for inconsistency, the I2=65% and point estimates of the two RCTs were in the opposite direction

f. We downgraded the quality of evidence by one level for imprecision; the CI included a substantial benefit and harm.

## Website, timeline Description automatically generated with medium confidenceEtD: Summary of judgements for fever treatment

## Type of recommendation



# 9. Should patients with CXR abnormalities, who develop a fever during their ICU stay, have a bedside thoracic ultrasound performed?

## Evidence profile

**Setting**: ICU

Bibliography: Winkler MH, Touw HR, van de Ven PM, Twisk J, Tuinman PR. Diagnostic Accuracy of Chest Radiograph, and When Concomitantly Studied Lung Ultrasound, in Critically Ill Patients With Respiratory Symptoms: A Systematic Review and Meta-Analysis. Crit Care Med. 2018;46(7):e707-e714. doi:10.1097/CCM.0000000000003129

**Pooled sensitivity**:0.95 (95% CI: 0.92 to 0.96)|**Pooled specificity**:0.94 (95% CI: 0.90 to 0.97)

| **Test result** | **Number of results per 1,000 patients tested (95% CI)** | | | **Number of participants  (studies)** | **Certainty of the Evidence (GRADE)** |
| --- | --- | --- | --- | --- | --- |
| **Prevalence10%**  Typically seen in | **Prevalence30%**  Typically seen in | **Prevalence50%**  Typically seen in |
| **True positives** | **95** (92 to 96) | **285** (276 to 288) | **475** (460 to 480) | 543 (10) | ⨁⨁◯◯ **Low**a,b |
| **False negatives** | **5** (4 to 8) | **15** (12 to 24) | **25** (20 to 40) |
| **True negatives** | **846** (810 to 873) | **658** (630 to 679) | **470** (450 to 485) | 543 (10) | ⨁⨁◯◯ **Low**a,b |
| **False positives** | **54** (27 to 90) | **42** (21 to 70) | **30** (15 to 50) |

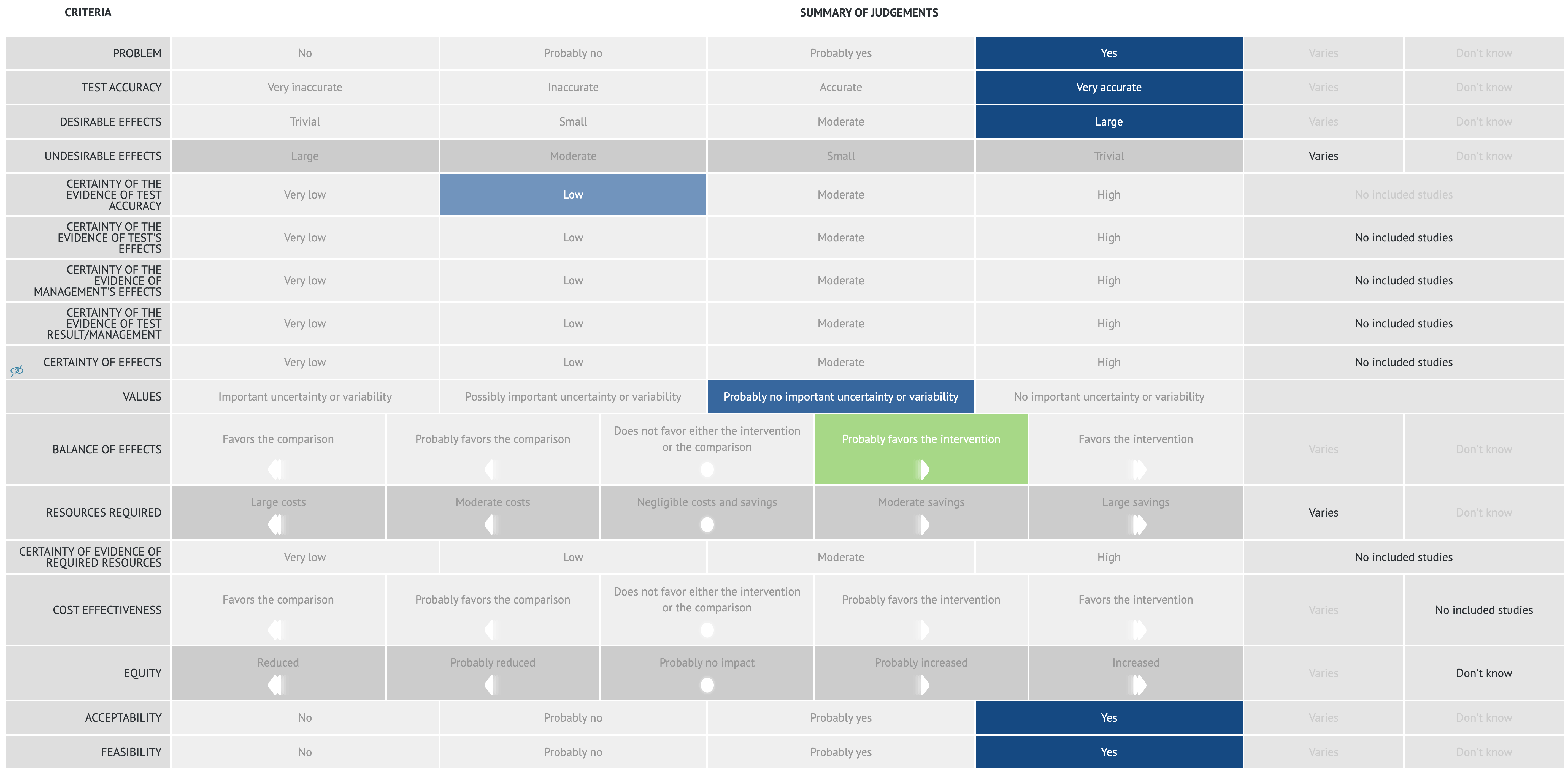
**CI:** confidence interval

#### Explanations

a. Most studies lacked in some way information about blind- ing to the reference standard while evaluating the index results or the other way around. Sometimes, this was mentioned, but mostly, it was simply not presented in the study.

b. Significant heterogeneity detected, I2 61.36 and 82.1 for sensitivity and specificity respectively.

## EtD: Summary of judgements for a bedside thoracic ultrasound in febrile patients with abnormal chest x-ray



## Type of recommendation

# 12. Should all patients with a fever in the ICU of at least 7 days duration without an established etiology have a 18F-FDG PET/CT?

## Evidence profile

**Setting**: ICU

Bibliography: Huang CK, Huang JY, Ruan SY, Chien KL. Diagnostic performance of FDG PET/CT in critically ill patients with suspected infection: A systematic review and meta-analysis. J Formos Med Assoc. 2020;119(5):941-949. doi:10.1016/j.jfma.2019.09.010

**Pooled sensitivity**:0.94 (95% CI: 0.79 to 0.99)|**Pooled specificity**:0.66 (95% CI: 0.45 to 0.83)

| **Test result** | **Number of results per 1,000 patients tested (95% CI)** | | | **Number of participants  (studies)** | **Certainty of the Evidence (GRADE)** |
| --- | --- | --- | --- | --- | --- |
| **Prevalence 10%**  Typically seen in | **Prevalence 30%**  Typically seen in | **Prevalence 50%**  Typically seen in |
| **True positives** | **94** (79 to 99) | **282** (237 to 297) | **470** (395 to 495) | 87 (4) | ⨁◯◯◯ **Very low**a,b |
| **False negatives** | **6** (1 to 21) | **18** (3 to 63) | **30** (5 to 105) |
| **True negatives** | **594** (405 to 747) | **462** (315 to 581) | **330** (225 to 415) | 4 (87) | ⨁◯◯◯ **Very low**a,b |
| **False positives** | **306** (153 to 495) | **238** (119 to 385) | **170** (85 to 275) |

**CI:** confidence interval

#### Explanations

a. We downgraded by 2 points for risk of bias due to "varied time periods between the standard and investigated test, varied reference method for confirming infection origin, dependence between the findings of the investigated and reference tests, lack of reporting for un-interpretable results and a lack of explanation for withdrawals. Verification bias was a major problem in these studies, in which the selection of the reference tests may be greatly influenced by the findings of the index test."

b. We downgraded for imprecision by 2 points as overall sample size very small (n=87) and very wide 95% CIs.

## EtD: Summary of judgements for 18F-FDG PET/CT

Graphical user interface

Description automatically generated with low confidence

## Type of recommendation

Application

Description automatically generated with medium confidence

# 17. Should rapid direct-from blood nucleic acid amplification tests be performed in febrile ICU patients (and if so, which one or ones)?

## Evidence profile

**Pooled sensitivity** : 0.83 (95% CI: 0.61 to 0.94) | **Pooled specificity** : 0.96 (95% CI: 0.84 to 0.99)

| **Test result** | **Number of results per 1,000 patients tested (95% CI)** | | | **Number of participants  (studies)** | **Certainty of the Evidence (GRADE)** |
| --- | --- | --- | --- | --- | --- |
| **Prevalence 10%**  Typically seen in | **Prevalence 20%**  Typically seen in | **Prevalence 50%**  Typically seen in |
| **True positives** | **83** (61 to 94) | **166** (122 to 188) | **415** (305 to 470) | 3711 (10) | ⨁◯◯◯ VERY LOW |
| **False negatives** | **17** (6 to 39) | **34** (12 to 78) | **85** (30 to 195) |
| **True negatives** | **864** (756 to 891) | **768** (672 to 792) | **480** (420 to 495) | 3711 (10) | ⨁◯◯◯ VERY LOW |
| **False positives** | **36** (9 to 144) | **32** (8 to 128) | **20** (5 to 80) |

**CI:** Confidence interval

| **Summary** |
| --- |
|
| One study (n=311 samples from 245 patients) compared multiplex PCR (VYOO(®) for 34 bacterial and 6 fungal species) and blood cultures for culture positivity, time to positivity and antibiotics appropriateness of antibiotics coverage. PCR detected more organisms (30.1% vs 14.5%), time to positivity was shorter (median, IQR) 24.2 (18.0, 27.5) vs 68 (52.2, 88.5). However, in PCR group 34% had inappropriate coverage. No difference in mortality. PCR sensitivity and specificity were 0.6 (95% confidence interval: 0.44-0.74) and 0.75 (0.69-0.8), respectively.(5)  One study (n=15 samples from 15 patients) compared Multiplex Tandem-PCR (MT-PCR, Bacterial Load Assay (AusDiagnostics)) vs quantitative PCR 16S rDNA and blood cultures. MT-PCR had sensitivity and specificity of 0.67 and 0.78 respectively.(6)  One study: (n= 1130 sample from 913 patients) compared Real-time PCR assays for beta-globin and Universal 16S rRNA gene targets in 1,120 paired sample samples. PCR has sensitivity of 77.8% (69.5 to 84.7), specificity of 99.3% (98.6 to 99.7) in detecting blood stream infections. Time to positivity was also significantly shorter with average difference of 74.1 h. (7.5 h compared to 27.9 ± 13.6 h for Gram stain or 81.6 ± 24.0 h for phenotypic identification).(7)  One study (n=1140 samples from 918 patients) compared Real-time PCR for DNA extracts for 16S rRNA and/or 23S rRNA gene targets to automated blood cultures. PCR had sensitivity, 90.9% (83.4–95.8%); specificity, 99.6% (99.0–99.9%). Time to positivity was also significantly shorter by approximately 14 hours.(8)  One study (n=49) compared 16S rRNA panbacterial polymerase chain reaction (PCR Aamp ® 96 DNA Blood Kit (Qiagen Pvt Ltd) to automated blood culture. Sensitivity and specificity were 100%, 91.8% respectively. The average time to positivity for automated blood culture was 12-48 h whereas that for PCR was about 4 h.(9)  One study (n=90) compared eubacterial PCR targeting 16S DNA sequence compared to automated blood culture Bactec 9050 instrument (Becton Dickinson). PCR had sensitivity and specificity of 100%, 43.33%, respectively. When restricted to patients who fulfilled criteria for sepsis, the sensitivity and specificity were 100% and 68.42%, respectively.(10)  One study (n=355 samples from 160 patients) compared two real-time PCR (TaqMan 7000 system, Sa442 DNA fragment of S. aureus and 16S rRNA genes of E. faecalis) assays for the quantitative detection of Staphylococcus aureus bacteremia and for Enterococcus faecalis to automated blood cultures. Combined sensitivity and specificity were 74% and 94.3% respectively.(11)  One study (n=55 samples from 45 patients) compared PCR detecting C. albicans, C. parapsilosis, C. tropicalis, C. dubliniensis C. glabrata, and C. krusei to blood cultures. PCR had sensitivity and specificity of 25% and 94.1% respectively.(12)  One study (n=32) compared . Multiplex polymerase chain reaction (PCR) was used (VYOO®, SIRS-Lab, Jena, Germany) and detected 11 of 32 blood culture proven candidemia. Sensitivity was 34%. Also, time to antifungals was reduced from 67.5 (52.4, 90) hours in the candida group, where candida infection was determined by blood culture, to 31.0 (28.0, 37.5; P < .01) hours in the PCR group.(13)  One study (n=513 samples from 157 patients) compared real-time PCR assays (Taqman) to blood cultured and had sensitivity, specificity, and positive and negative predictive values of the assays in this trial were 90.9%, 100%, 100% and 99.8%, respectively.(14) |

## Graphical user interface Description automatically generated with medium confidenceEtD: Summary of judgements for direct-from blood nucleic acid amplification tests

## Type of recommendation

# 23. Should patients with pneumonia in the ICU with signs or symptoms of respiratory pathology be tested for viral pathogens and if so, how?

## Evidence Profile

| **Summary** |
| --- |
|
|  One study (n=52) Compared the yield of paired nasopharyngeal aspirates or nose–throat swab (NTS) and endotracheal aspirate (EA) specimens taken simultaneously as the first diagnostic sample for detection of influenza viral RNA by real-time reverse transcriptase polymerase chain reaction (rRT-PCR) in patients admitted to adult ICUs. 22 positive influenza. Both 12; NTS only 2; EA only 8. For optimal diagnosis of influenza in ICU patients use EA, but include NTS where possible.(15)   One study (n=414) evaluated the frequency of respiratory viruses was evaluated in respiratory samples collected from patients with CAP admitted to 26 ICUs. In 226 (54.6%) patients one or more respiratory viruses were identified, while 188 (45.4%) patients were negative. A single virus infection was observed in 214/226 (94.7%) patients; while, in 12/226 (5.3%) at least two respiratory viruses were detected. Influenza A was the most common virus in 140/226 patients (61.9%) followed by rhinoviruses (33/226, 14.6%), respiratory syncytial virus (13/226, 5.8%), influenza B virus (9/226, 4.0%), human coronaviruses (9/226, 4.0%), cytomegalovirus (9/226, 4.0%) and human metapneumovirus (1/226, 0.4%). Viral infections are present in a consistent proportion of patients admitted to the ICU for CAP. Influenza A and rhinovirus accounted for three-quarters of all CAP in ICU patients. The use of lower respiratory instead of upper respiratory samples might be useful in the diagnosis of viral CAP.(16)   One study (n=999). Assessed proportion of respiratory viruses and their impact on the outcome of hospital-acquired pneumonia (HAP) in the intensive care unit (ICU). Respiratory viruses were detected in 32% of HAP patients who underwent multiplex PCR. Two situations were encountered: (i) acute acquired viral infection; (ii) long-term viral carriage (mostly rhinovirus) especially in immunocompromised patients complicated by a virus/bacteria coinfection. The latter was associated with a longer length of stay and a trend toward a higher mortality.(17)   One study (n=47 BAL samples from 41 patients) acute pneumonia attending an intensive care unit. By molecular diagnosis, 30% of total BAL and 63% of bacteria-negative BAL were positive for respiratory viruses. Molecular detection allows for high-rate detection of respiratory viral infections in adult patients suffering from severe pneumonia.(18)   One study: (n=139) Respiratory specimens were tested in culture, indirect immunofluorescence assay, and PCR or RT-PCR for virological assessment. Patients were followed until ICU discharge or death. Upon enrollment, a respiratory virus was detected in the tracheobronchial aspirate in 25% of patients (35 of 139). The incidence of VAP, defined according to clinical daily evaluation, was 28% (39 of 139 patients). A bacteria was documented in 74% of cases, whereas no case of a causative viral infection was encountered among VAP patients; however, herpes simplex virus type-1 (HSV 1) infection was detected in respiratory specimens of 31% of VAP (12 of 39). A high incidence of HSV-1 infection in VAP patients was found; however, nosocomial viral VAP is likely to be rare in ICU, as assessed by the absence of respiratory virus-induced VAP identified in this prospective cohort study.(19)   One study (n=105) in COPDER patients older than 45 years admitted to ICU for noninvasive or invasive ventilation. Nasopharyngeal aspirates (NPA) and posterior pharyngeal swabs (PS) were tested for viruses with immunofluorescence assay (IFA), virus culture (VC) and polymerase chain reaction (PCR). Paired virus and atypical pneumonia serology assays were taken. Blood, sputum and endotracheal aspirates were cultured for bacteria. Forty-six (43%) of the patients with COPD exacerbation requiring mechanical ventilation had a probable viral pathogen. Prodromal, clinical and outcome parameters did not distinguish virus from non-virus illness. PCR was the most sensitive while viral culture was the least of virus assays.(20)   One study (n=70) Investigated the burden of viral infections in non-immunocompromised patients admitted to the intensive care unit for acute respiratory failure using a multiplex molecular assay (Respi-Finder19). Patients were investigated for respiratory viruses using immunofluorescence testing and a commercial multiplex molecular assay, and for bacteria using conventional culture. Half the patients (34/70, 49%) had a documented RV infection. No other pathogen was found in 24 (71%) patients. Viral infection was detected more frequently in patients with obstructive respiratory diseases (64% vs. 29%; P = 0.0075). Multiplex molecular assay should be considered as an useful diagnostic tool in patients admitted to the intensive care unit with acute respiratory failure, especially those with acute exacerbations of chronic obstructive pulmonary disease and asthma.(21)   One study (n=100) Cohort study of patients with severe CAP in an intensive care unit, endotracheal aspirates for intubated patients and nasopharyngeal swabs for non-intubated patients were sent for PCR amplification for respiratory viruses (Seeplex RV12 detection kit). Blood, endotracheal aspirates for intubated patients, and sputum for non-intubated patients were analyzed using a multiplex PCR system for bacteria. Out of 100 patients, using predominantly cultures, bacteria were identified in 42 patients; PCR amplification increased this number to 55 patients. PCR amplification identified viruses in 32 patients. In total, only bacteria, only viruses, and both bacteria and viruses were found in 37, 14, and 18 patients, respectively. The commonest viruses were influenza A H1N1/2009 and rhinovirus; the commonest bacterium was Streptococcus pneumoniae. Hospital mortality rates for patients with no pathogens, bacterial infection, viral infection, and bacterial-viral co-infection were 16.1, 24.3, 0, and 5.6%, respectively (p = 0.10). On multivariable analysis, virus detection was associated with lower mortality (adjusted odds ratio 0.12, 95% confidence interval 0.2-0.99; p = 0.049). Viruses and bacteria were detected in 7 of 10 patients with severe CAP with the aid of PCR amplification. Viral infection was independently associated with lower mortality.(22)   One study (n=100) Prospective single-center study to assess the sensitivity and clinical relevance of molecular testing for respiratory viruses in critically ill immunocompromised patients with acute respiratory failure. Nasopharyngeal aspirates and/or bronchoalveolar lavage fluid were tested for respiratory viruses using both the MMA and immunofluorescence. A virus was detected in 47 (47%) patients using the MMA and 8 (8%) patients using immunofluorescence (P = 0.006). MMA-positive and MMA-negative patients had similar clinical and radiographic presentations and were not significantly different for the use of ventilatory support (58% vs. 76%, P = 0.09), occurrence of shock (43% vs. 53%, P = 0.41), use of renal replacement therapy (26% vs. 23%, P = 0.92), SAPS II (35 [26-44] vs. 38 [27-50], P = 0.36), time spent in the ICU (6 vs. 7 days, P = 0.35), or ICU mortality (17% vs. 28%, P = 0.27). Using MMA, a virus was found in 6 of the 12 patients with no diagnosis at the end of the etiologic investigations. MMA was far more sensitive than immunofluorescence for respiratory virus detection. Patients with RVs detected in the respiratory tract had the same clinical characteristics and outcomes as other patients.(23)   One study (n=174) to determine the prevalence of herpes virus DNA in respiratory secretions in patients on mechanical ventilation. Respiratory secretions taken thrice weekly from patients in a tertiary center intensive therapy unit (ITU) were tested for herpes simplex virus (HSV) by nested PCR. Samples from 61 patients in ITU for 4 days or more were also tested for Epstein Barr Virus (EBV) and cytomegalovirus (CMV) using real-time PCR. HSV positivity increased with ITU stay with 18.6% admission samples positive, 32.5% day 2-5 samples, and 65.9% day 6-39 samples. Being HSV positive on admission did not influence mortality (9/27, 33.3% vs. 38/118, 32.2%) however, subsequently, mortality of those negative but becoming positive was higher than in those remaining negative (10/35, 29% vs. 5/24 21%). At least one sample was EBV positive in 61% and CMV positive in 19% of patients tested. Of 63 patients tested for all three viruses, 4 were positive for three viruses, 23 patients for two viruses, 24 for one virus and 12 were negative for all the above viruses. Detection of HSV, EBV and CMV is common in ITU patients. Becoming HSV positive while in ITU may increase mortality.(24)   One study (n=348 BAL samples from 290 patients) 18-bed general intensive care unit (ICU) of the Maastricht University Medical Centre in The Netherlands. All consecutive BALF samples obtained from critically ill patients clinically suspected of HAP were included. An in-house real-time polymerase chain reaction (PCR) was used for detection of hMPV RNA. Human metapneumovirus RNA was detected in 6 out of 348 (1.7%) BALF samples. All six patients were immunocompromised and developed respiratory insufficiency necessitating ICU admittance. BAL performed during their stay in the ICU did not reveal bacterial HAP.(25)   One study (n=747) assessed the association between viral detection in nasopharyngeal swabs and ICU mortality in critically ill hematology patients. Of the 747 patients (447 with acute respiratory failure [ARF]), 21.3% had a virus detected (56.4% rhinovirus/enterovirus and 30.7% influenza/parainfluenza/respiratory syncytial viruses). Overall ICU and hospital mortality rates were 26% and 37%, respectively. Assay positivity was associated with lymphoproliferative disorders, hematopoietic stem cell transplantation, treatment with steroids or other immunosuppressants, ARF (25.5% vs. 16.3%; P = 0.004), and death in the ICU (28.9% vs. 19.3%; P = 0.008). The association with ICU mortality was significant for all viruses and was strongest for influenza/parainfluenza/respiratory syncytial viruses. In patients with ARF, detection of any respiratory virus was independently associated with ICU mortality (odds ratio, 2.07; 95% confidence interval, 1.22–3.50).(26) |

## Timeline Description automatically generated with low confidenceEtD: Summary of judgements testing for viral pathogens

## Type of recommendation

Graphical user interface, application

Description automatically generated

# 24. In adult, critically ill patients with a new fever and no clear focus of infection, should we recommend measuring serum procalcitonin in addition to bedside evaluation versus bedside clinical evaluation alone?

## Evidence profile

**Bibliography:** Tan M, Lu Y, Jiang H, Zhang L. The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis.(27)

**Pooled sensitivity** : 0.80 (95% CI: 0.69 to 0.87) | **Pooled specificity** : 0.77 (95% CI: 0.60 to 0.88)

| **Test result** | **Number of results per 1,000 patients tested (95% CI)** | | | **Number of participants  (studies)** | **Certainty of the Evidence (GRADE)** |
| --- | --- | --- | --- | --- | --- |
| **Prevalence 10%**  Typically seen in | **Prevalence 20%**  Typically seen in the ICU | **Prevalence 40%**  Typically seen in |
| **True positives** | **80** (69 to 87) | **160** (138 to 174) | **320** (276 to 348) | 1368 (10) | ⨁◯◯◯ **VERY LOW** a,b |
| **False negatives** | **20** (13 to 31) | **40** (26 to 62) | **80** (52 to 124) |
| **True negatives** | **693** (540 to 792) | **616** (480 to 704) | **462** (360 to 528) | 1368 (10) | ⨁◯◯◯ **VERY LOW** a,b |
| **False positives** | **207** (108 to 360) | **184** (96 to 320) | **138** (72 to 240) |

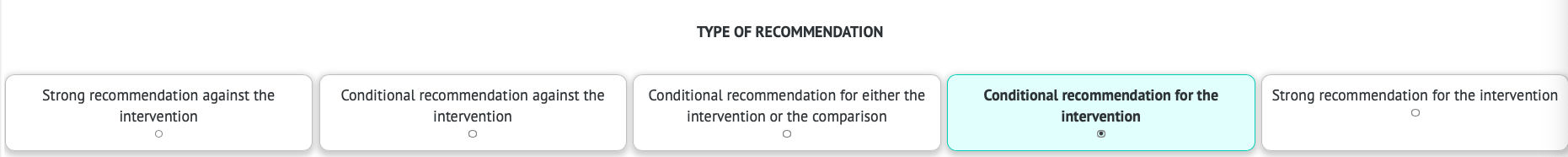
#### Explanations

a. We downgraded the quality of evidence by one level for serious indirectness, in these studies the population were mostly patients with SIRS (not fever), it is possible that the diagnostic accuracy of the index test would change in different population

b. We downgraded the quality of evidence by one level for serious imprecision, the CI included values below the acceptable diagnostic threshold

## Graphical user interface, application Description automatically generatedEtD for serum procalcitonin

## Type of recommendation



# **25**. In adult, critically ill patients with a new fever and no clear focus of infection, should we recommend measuring C-reactive protein in addition to bedside evaluation versus bedside clinical evaluation alone?

## Evidence profile

**Bibliography:** Tan M, Lu Y, Jiang H, Zhang L. The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis.(27)

**Pooled sensitivity** : 0.80 (95% CI: 0.63 to 0.90) | **Pooled specificity** : 0.61 (95% CI: 0.50 to 0.72)

| **Test result** | **Number of results per 1,000 patients tested (95% CI)** | | | **Number of participants  (studies)** | **Certainty of the Evidence (GRADE)** |
| --- | --- | --- | --- | --- | --- |
| **Prevalence 10%**  Typically seen in | **Prevalence 20%**  Typically seen in | **Prevalence 40%**  Typically seen in |
| **True positives** | **80** (63 to 90) | **160** (126 to 180) | **320** (252 to 360) | 1368 (10) | ⨁◯◯◯ **VERY LOW** a,b |
| **False negatives** | **20** (10 to 37) | **40** (20 to 74) | **80** (40 to 148) |
| **True negatives** | **549** (450 to 648) | **488** (400 to 576) | **366** (300 to 432) | 1368 (10) | ⨁◯◯◯ **VERY LOW** a,b |
| **False positives** | **351** (252 to 450) | **312** (224 to 400) | **234** (168 to 300) |

a. We downgraded the quality of evidence by one level for serious indirectness, in these studies the population were mostly patients with SIRS (not fever), it is possible that the diagnostic accuracy of the index test would change in different population

b. We downgraded the quality of evidence by one level for serious imprecision, the CI included values below the acceptable diagnostic threshold

## Graphical user interface Description automatically generatedEtD for CRP

## Type of recommendation

# References:

1. Niven DJ, Gaudet JE, Laupland KB, et al. Accuracy of peripheral thermometers for estimating temperature: a systematic review and meta-analysis. Ann Intern Med 2015;163(10):768-777.

2. Poveda VB, Nascimento AS. Intraoperative body temperature control: esophageal thermometer versus infrared tympanic thermometer. Rev Esc Enferm USP 2016;50(6):946-952.

3. Furlong D, Carroll DL, Finn C, et al. Comparison of temporal to pulmonary artery temperature in febrile patients. Dimens Crit Care Nurs 2015;34(1):47-52.

4. Sakkat A, Alquraini M, Aljazeeri J, et al. Temperature control in critically ill patients with fever: A meta-analysis of randomized controlled trials. J Crit Care 2021;61:89-95.

5. Bloos F, Sachse S, Kortgen A, et al. Evaluation of a polymerase chain reaction assay for pathogen detection in septic patients under routine condition: an observational study. PLoS One 2012;7(9):e46003.

6. Ginn AN, Hazelton B, Shoma S, et al. Quantitative multiplexed-tandem PCR for direct detection of bacteraemia in critically ill patients. Pathology 2017;49(3):304-308.

7. Moore MS, McCarroll MG, McCann CD, et al. Direct Screening of Blood by PCR and Pyrosequencing for a 16S rRNA Gene Target from Emergency Department and Intensive Care Unit Patients Being Evaluated for Bloodstream Infection. J Clin Microbiol 2016;54(1):99-105.

8. McCann CD, Moore MS, May LS, et al. Evaluation of real-time PCR and pyrosequencing for screening incubating blood culture bottles from adults with suspected bloodstream infection. Diagn Microbiol Infect Dis 2015;81(3):158-162.

9. Gupta MD, Kaur H, Ray P, et al. Ribosomal RNA-based panbacterial polymerase chain reaction for rapid diagnosis of septicaemia in Intensive Care Unit patients. Indian J Med Microbiol 2016;34(2):219-221.

10. Rowther FB, Rodrigues CS, Deshmukh MS, et al. Prospective comparison of eubacterial PCR and measurement of procalcitonin levels with blood culture for diagnosing septicemia in intensive care unit patients. J Clin Microbiol 2009;47(9):2964-2969.

11. Peters RP, van Agtmael MA, Gierveld S, et al. Quantitative detection of Staphylococcus aureus and Enterococcus faecalis DNA in blood to diagnose bacteremia in patients in the intensive care unit. J Clin Microbiol 2007;45(11):3641-3646.

12. McMullan R, Metwally L, Troughton JA, et al. The impact of a PCR assay for candidemia on antifungal drug prescribing in critical care: an interrupted time series pilot study. J Infect 2010;61(1):81-85.

13. Bloos F, Bayer O, Sachse S, et al. Attributable costs of patients with candidemia and potential implications of polymerase chain reaction-based pathogen detection on antifungal therapy in patients with sepsis. J Crit Care 2013;28(1):2-8.

14. McMullan R, Metwally L, Coyle PV, et al. A prospective clinical trial of a real-time polymerase chain reaction assay for the diagnosis of candidemia in nonneutropenic, critically ill adults. Clin Infect Dis 2008;46(6):890-896.

15. Lopez Roa P, Rodriguez-Sanchez B, Catalan P, et al. Diagnosis of influenza in intensive care units: lower respiratory tract samples are better than nose-throat swabs. Am J Respir Crit Care Med 2012;186(9):929-930.

16. Piralla A, Mariani B, Rovida F, et al. Frequency of respiratory viruses among patients admitted to 26 Intensive Care Units in seven consecutive winter-spring seasons (2009-2016) in Northern Italy. J Clin Virol 2017;92:48-51.

17. Loubet P, Voiriot G, Houhou-Fidouh N, et al. Impact of respiratory viruses in hospital-acquired pneumonia in the intensive care unit: A single-center retrospective study. J Clin Virol 2017;91:52-57.

18. Legoff J, Guerot E, Ndjoyi-Mbiguino A, et al. High prevalence of respiratory viral infections in patients hospitalized in an intensive care unit for acute respiratory infections as detected by nucleic acid-based assays. J Clin Microbiol 2005;43(1):455-457.

19. Daubin C, Vincent S, Vabret A, et al. Nosocomial viral ventilator-associated pneumonia in the intensive care unit: a prospective cohort study. Intensive Care Med 2005;31(8):1116-1122.

20. Cameron RJ, de Wit D, Welsh TN, et al. Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. Intensive Care Med 2006;32(7):1022-1029.

21. Schnell D, Gits-Muselli M, Canet E, et al. Burden of respiratory viruses in patients with acute respiratory failure. J Med Virol 2014;86(7):1198-1202.

22. Siow WT, Koay ES, Lee CK, et al. The Use of Polymerase Chain Reaction Amplification for the Detection of Viruses and Bacteria in Severe Community-Acquired Pneumonia. Respiration 2016;92(5):286-294.

23. Schnell D, Legoff J, Mariotte E, et al. Molecular detection of respiratory viruses in immunocopromised ICU patients: incidence and meaning. Respir Med 2012;106(8):1184-1191.

24. Smith CA, Conroy LT, Pollock M, et al. Detection of herpes viruses in respiratory secretions of patients undergoing artificial ventilation. J Med Virol 2010;82(8):1406-1409.

25. Vanspauwen MJ, van Mook WN, Bruggeman CA, et al. Human metapneumovirus in bronchoalveolar lavage fluid of critically ill patients with suspected pneumonia. Intensive Care Med 2012;38(4):728-729.

26. Legoff J, Zucman N, Lemiale V, et al. Clinical Significance of Upper Airway Virus Detection in Critically Ill Hematology Patients. Am J Respir Crit Care Med 2019;199(4):518-528.

27. Tan M, Lu Y, Jiang H, et al. The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis. J Cell Biochem 2019;120(4):5852-5859.