**Supplementary Table 1. Search Strategy**

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| --- | --- |
| Medline | Embase |
| Biological Markers terms:1. Biological markers
2. Biomarkers
3. Calcitonin
4. Procalcitonin
 | Biological Markers terms:1. Procalcitonin
 |
| ICU Terms and Specific Infection and Sepsis Terms 1. Sepsis
2. Bacteremia
3. Pneumonia, Ventilator-Associated
4. Pneumonia
5. Shock, Septic
6. Intensive Care Units
7. Critical Care
8. Critical Care Unit
9. Critical Illness
 | ICU Terms and Specific Infection and Sepsis Terms 1. Sepsis
2. Bacteremia
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4. Pneumonia
5. Shock, Septic
6. Intensive Care Units
7. Critical Care
8. Critical Care Unit
9. Critical Illness
 |
| Antibiotic Terms 1. Antibiotics
2. Anti-Bacterial agents
 | Antibiotic Terms 1. Antibiotics
 |

**Supplementary Table 2. Characteristics of included studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author / Year (Country)****(PCT assay / manufacturer)** | **N** **(PCT / Control)** | **Design** | **Setting** | **PCT algorithm** | **Overruling** | **Outcome (PCT vs. control)** | **Comments** |
| **Studies using PCT-guided algorithms for initiation of antibiotic therapy** |
| Jensen, 2011 (Denmark)(Kryptor PCT / Brahms) | 604 / 596 | P, R, MC, OL | Mixed ICU | - PCT > 1 mcg/L that was not decreasing at least 10% from previous day prompted increase in antimicrobial spectrum and diagnostic efforts | 17.9% (only available for BL PCT) | - 28-day mortality: 31.5% vs. 32 % (p=0.98)- ICU LOS: 6 vs. 5 days (p=0.004)- ICU days with MV: 65.5% vs. 60.7% (p<0.001)- ICU days with at least 3 antimicrobials: 65.5% vs. 57.7% (p<0.001) | - PCT did not improve outcomes, and may have increased ICU LOS, MV use, and antimicrobial use- Increase morbidity may have been associated with increased use of antimicrobials  |
| Layios, 2012(Beligum)(Kryptor PCT / Pasteur Mérieux) | 258 / 251 | P, R, SC, OL | Mixed ICU | - PCT < 0.25 mcg/L: ABX strongly discouraged- PCT between 0.25 – 0.5 mcg/L: ABX discouraged- PCT between 0.5 – 1.0 mcg/L: ABX encouraged- PCT > 1.0 mcg/L: ABX strongly encouraged | PCT > 1 mcg/L: 11.4%PCT 0.5-1 mcg/L: 23.1%PCT: 0.25 – 5 mcg/L: 80.9%PCT: <0.25 mcg/L: 53.7% | - ICU days with ABX use: 62.6 ± 34.4% vs. 57.7 ± 34.4% (p=0.11)- ICU mortality and LOS similar between groups | - PCT not associated with improvements in outcomes or ABX consumption- compliance with reserving ABX therapy was poor  |
| Nafaji, 2015 (Iran)(Kryptor PCT / Brahms) | 30 / 30 | P, R, SC, SB | Mixed ICU | - PCT < 0.5 mcg/L: ABX discouraged, PCT rechecked after 12 hours - PCT between 0.5-2 mcg/L: ABX held, PCT rechecked after 8 hours - PCT >2 mcg/L: ABX encouraged(rechecked PCT > 2 mcg/L: ABX encouraged) | NR | - Total ABX exposure lower with PCT guidance (128 days vs. 320 days, p=0.003)- ICU LOS: 4 vs. 6days, p=0.01- Hospital mortality and hospital LOS similar between groups | - PCT associated with decrease ABX use with no worsening of mortality  |
| **Studies using PCT-guided algorithms for cessation of antibiotic therapy** |
| Bloos, 2016 (Germany)(NR) | 552 / 537 | P, R, MC, OL | Mixed ICU | PCT checked at BL; day 4, 7, 10, and 14. - Day 7-14 PCT < 1 mcg/L or >50% drop from previous PCT: ABX stopped | Day 7: 59%Day 10: 61% | - No difference in 28d mortality (25.6% vs. 28.2%, p=0.34)- 4.5% reduction in ABX exposure with PCT guidance | -2x2 factorial study with selenium. Significant interaction detected between PCT and selenium, where selenium administration seemed to harm patients not receiving PCT guidance |
| De Jong, 2016 (Netherlands)(Krpytor PCT / Thermo Fisher or Vidas or Roche) | 761 / 785 | P, R, MC, OL | Mixed ICU | - PCT decreased by >80% of peak or absolute value <0.5 mcg/L: ABX stopped | 24h: 56%48h: 47%End of study: 3% | - significant difference in ABX use and median ABX duration- significant decrease in mortality (20% vs. 25%, p=0.012) | - 1 year mortality difference observed in per protocol population (36% vs. 43%, p=0.019) |
| Deliberato, 2013 (Brazil)(Vidas PCT / bioMérieux) | 42 / 39 | P, R, SC, OL | Mixed ICU | - BL PCT ≥1 mcg/L, re-evaluation at day 5, and ABX stopped if PCT < 10% of BL level or < 0.25 mcg/L- BL PCT <1 mcg/L, re-evaluation at day 3 and ABX were stopped if PCT < 0.1 mcg/L | 29% (personal communication) | - ABX duration (per-protocol ): 9 vs. 13 days (p=0.008)- Hospital mortality: 2.4% vs. 10.3%- ICU LOS: 3.5 vs. 3 days (p=0.60) | - PCT shortened duration of ABX without worsening mortality - Majority of patients met criteria for severe sepsis |
| Hochreiter, 2009 (Germany)(Brahams PCT / Brahms) | 57 / 53 | P, R, SC, OL | SICU | - PCT < 1 mcg/L or dropped to 25-35% of the BL value over 3 days | NR | - Duration of ABX: 5.9 vs. 7.9 days (p<0.001)- Hospital mortality: 26.3% vs. 26.4% (p = NS)ICU LOD: 15.5 vs. 17.7 days (p=0.046) | - PCT shortened duration of ABX without worsening mortality- Patients met criteria for sepsis |
| Nobre, 2008(Switzerland)(Kryptor PCT / Brahms) | 39 / 40 | P, R, SC, OL | Mixed ICU | - BL PCT ≥1 mcg/L, re-evaluation at day 5, and ABX stopped if PCT < 10% of BL level or < 0.25 mcg/L- BL PCT <1 mcg/L, re-evaluation at day 3 and ABX were stopped if PCT < 0.1 mcg/L | 19% | - Duration of ABX (all patients) : 6 vs. 9.5 days (p=0.15)- Duration of ABX (compliant to protocol): 6 vs. 12.5 days (p<0.001)- 28d mortality: 20.5% vs. 20% (p=0.82)ICU LOS: 4 vs. 7 days (p=0.02) | - PCT shortened duration of ABX without worsening mortality- Compliance with protocol led to statistical significant difference in ABX duration |
| Oliveira, 2013 (Brazil) (Vidas PCT / bioMérieux) | 49 / 45 | P, R, MC, OL | Mixed ICU | PCT assessed on day 3:- If < 1 mcg/L, PCT checked daily and ABX stopped when PCT < 0.1 mcg/L- If >1 mcg/L, PCT checked daily and AB stopped when PCT decrease > 90%  | 14% | - no difference in median duration of ABX: 7d vs 6d (p-0.13)- no difference in end of study mortality  | - Control group – C-reactive protein guidance |
| Schroeder, 2009 (Germany) | 14 / 13 | P, R, SC, OL | SICU | - PCT < 1 mcg/L or decreased to 25-35% of the BL value over 3 days | NR | - Duration of ABX: 6.6 vs. 8.3 days (p<0.001)- Hospital mortality: 21.4% vs. 23.1% (p = NS)ICU LOS: 16.4 vs. 16.7 days (p=NS) | - PCT shortened duration of ABX without worsening mortality- Patients met criteria for severe sepsis / septic shock |
| Shehabi, 2014 (Australia)(Brahams PCT / Brahms) | 196 / 196 | P, R, MC, SB | Mixed ICU | - Cease ABX for any of the following: - PCT < 0.1 mcg/L - PCT 0.1-0.25 mcg/L and infection is highly unlikely - PCT level decreased > 90% from initial value | 3% | - median time to ABX cessation: 9 vs. 11days, p=0.58- No difference detected in ICU or hospital LOS, MV time, or mortality | - PCT did not affect ABX duration- Protocol was most conservative and allowed for clinician assessment without violation |
| Stolz, 2009 (Switzerland, United States)(Kryptor PCT / Brahms) | 51 / 50 | P, R, MC, OL | Mixed ICU | - PCT < 0.25 mcg/L: ABX strongly discouraged- PCT between 0.25 – 0.5 mcg/L or decrease 80% from BL: ABX - discouraged- PCT between 0.5 – 1.0 mcg/L: ABX encouraged- PCT > 1.0 mcg/L: ABX strongly encouraged | 16% | - Day 28 ABX-free days: 13 vs. 9.5 (p=0.038)- Day 28 MV-free days: 21 vs. 19 (p=0.46)- Day 28 ICU-free days: 10 vs. 8.5 (p=0.53)- Day 28 mortality: 16% vs. 24% (p=0.33) | - PCT shortened duration of ABX without worsening mortality - Patients all met criteria for VAP  |
| **Studies using PCT-guided algorithms for both initiation and cessation of antibiotic therapy** |
| Annane, 2013 (France)(Brahams PCT / Brahms) | 30 / 28 | P, R, MC, OL | Mixed ICU | Medical patients - PCT < 0.25 mcg/L: ABX not recommended- PCT between 0.25 – 0.5 mcg/L: ABX strongly discouraged- PCT between 0.5 – 5.0 mcg/L: ABX recommended- PCT ≥ 5.0 mcg/L: ABX strongly recommendedSurgical patientsPCT < 4.0 mcg/L: ABX not recommended- PCT between 4.0 – 9.0 mcg/L: ABX recommended- PCT ≥ 9.0 mcg/L: ABX strongly encouraged | 19% at 6 hours17% at day 337% at day 5 | - Day 5 ABX use: 67% vs. 81% (p=0.24)- no difference observed in ICU LOS, hospital LOS, or mortality | - Study terminated prematurely due to low recruitment rate- compliance was poor among patients with low BL PCT |
| Bouadma, 2010 (France)(Kryptor PCT / Brahms) | 307 / 314 | P, R, MC, OL, NI | Mixed ICU | Baseline PCT value to determine whether ABX should be started and serial PCT values to decide if ABX should be stopped- PCT < 0.25 mcg/L: ABX strongly discouraged- PCT between 0.25 – 0.5 mcg/L or decrease 80% from BL: ABX - discouraged- PCT between 0.5 – 1.0 mcg/L: ABX encouraged- PCT > 1.0 mcg/L: ABX strongly encouraged | 53% | - Day 28 mortality: 21.2% vs. 20.4%, met non-inferiority criteria- Day 28 ABX-free days: 14.3 vs. 11.6 (p<0.001) | - PCT shortened duration of ABX use- Non-compliance to protocol was high, and largely due to reluctance to hold initial antibiotics |
| Ding, 2013 (China)(Kryptor PCT / Brahms) | 33 / 35 | P, R, MC, OL | Medical ICU | - ABX continued until PCT ≤ 0.5 mcg/L | 0% (patients with protocol violation were removed from study) | - Significant reduction in ABX duration (8.7d vs 14.2d, p<0.001)- no difference in mortality, duration of MV, or hospital LOS | - Patients with acute exacerbations of IPF |

ABX, antibiotics; BL, baseline; D, day; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis, LOS, length of stay; MC, multi-center; MV, mechanical ventilation; N, number; NI, non-interiority; NR, not reported; NS, not significant; OL, open-label; P, prospective; PCT, procalcitonin; R, randomized; SB, single-blinded; SC, single center; SICU, surgical intensive care unit

 **Supplementary Figure 1. Risk of Bias Summary**

Initiation

Cessation

Mixed

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias | Overall risk of bias |
| Jensen 2011 | + | + | - | ? | + | + | + | + |
| Layios 2012 | ? | ? | - | + | + | + | + | + |
| Nafaji 2015 | + | ? | - | ? | ? | ? | + | - |
| Bloos 2016 | + | + | - | + | + | + | + | + |
| de Jong 2016 | + | + | - | ? | + | + | + | + |
| Deliberato 2013 | ? | ? | - | ? | + | + | + | ? |
| Hochreiter 2009 | ? | ? | - | ? | + | ? | ? | ? |
| Nobre 2008 | + | + | - | - | + | + | + | ? |
| Oliveira 2013 | + | + | - | ? | + | - | + | ? |
| Schroeder 2009 | ? | ? | - | ? | + | ? | + | ? |
| Shehabi 2014 | + | + | - | ? | + | + | + | + |
| Stolz 2009 | + | + | - | ? | + | + | + | + |
| Annane 2013 | + | + | - | ? | + | + | + | + |
| Boudama 2010 | + | + | - | + | + | + | + | + |
| Ding 2013 | + | - | ? | ? | - | + | + | - |

Cochrane Collaboration tool for assessing risk of bias for each study. + low risk of bias; - high risk of bias; ? unclear risk of bias.

**Supplementary Figure 2. Funnel plot of included studies: short term, all cause mortality**



**Supplementary Figure 3. Forest plot – long-term mortality (Cessation subgroup only)**

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 **Supplementary Figure 4. Forest plot – hospital length of stay** **(Cessation Subgroup Only)**

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**Supplementary Figure 5. Forest plot – ICU length of stay** 

**Supplementary Figure 6. Forest plot – Recurrent infections (Cessation subgroup only)**

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**Supplementary Figure 7. Forest Plot - Sensitivity analysis – Short term mortality (28d only)**

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**Supplementary Figure 8. Forest Plot - Sensitivity analysis – Short term mortality (Studies with low risk of bias)**

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