Online appendices

Table of Contents

Appendix 1. Search Strategies

a. Medline (OVID) and Cochrane Library

Procalcitonin

1 procalcitonin.rn

2 procalcitonin.tw

3 pro-calcitonin.tw

4 calcitonin precursor$.tw

5 OR/1-4

Chronic Obstructive Pulmonary Disease

6 exp Chronic Obstructive Pulmonary Disease/

7 Lung diseases, obstructive/

8 exp Emphysema/

9 exp Chronic bronchitis/

10 COPD.tw

11 COAD.tw

12 (chronic adj2 bronchitis).tw

13 Emphysema.tw

14 (obstructive adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw

15 OR/6-14

16 5 AND 15

b. EMBASE (Ovid)

Procalcitonin

1 exp procalcitonin/

2 procalcitonin.tw

3 pro-calcitonin.tw

4 calcitonin precursor$.tw

5 OR/1-4

Chronic Obstructive Pulmonary Disease

6 exp Chronic Obstructive Pulmonary Disease/

7 exp Emphysema/

8 exp Chronic bronchitis/

9 COPD.tw

10 COAD.tw

11 (chronic adj2 bronchitis).tw

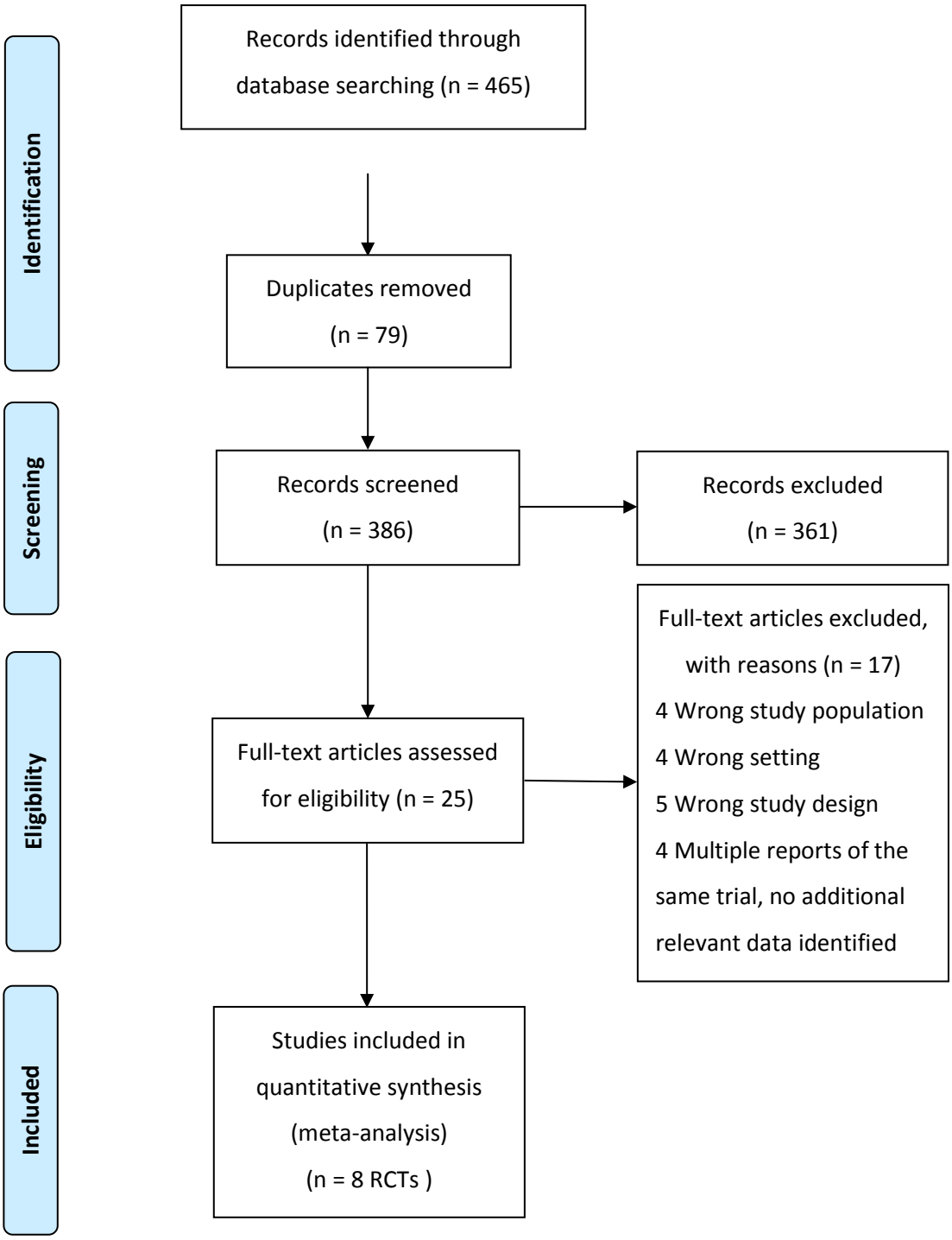
12 Emphysema.tw

13 (obstructive adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw

14 OR/6-13

15 5 AND 14

Appendix 2. PRISMA Flow diagram



Appendix 3. Characteristics of the included studies

Christ-Crain 2004
Reference: Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet (London, England). 2004;363(9409):600-7.

Methods	Cluster-randomized controlled, single blinded trial. 243 patients with suspected lower respiratory tract infections, including 60 patients with acute exacerbations of COPD were randomized from the medical emergency department of the University Hospital in Basel, Switzerland, between December 2002 and April 2003. The trial was powered to detect a 30% reduction in antibiotic exposure (two-tailed test, 5% significance, not powered especially for patients presenting with acute exacerbations of COPD).
Participants	Patients attending the emergency department with cough, dyspnoea or both, with a suspicion of lower respiratory tract infection as the main diagnosis were assessed for inclusion. Exclusion criteria: Severely immunocompromised patients (i.e. with HIV infection and a CD4 count less than 200 cells per mL, neutropenic patients and stem cell transplant recipients), cystic fibrosis, active tuberculosis, individuals with hospital acquired pneumonia. COPD was defined according to GOLD, as an FEV_1/FVC ratio of <70% predicted.
Interventions	In all cases, diagnostic and treatment decisions were left to the discretion of the treating doctor. In the procalcitonin group, antibiotics were strongly discouraged for procalcitonin levels <0.1µg/L, discouraged for procalcitonin between 0.1 and 0.25µg/L, encouraged for levels between 0.25-0.5µg/L and strongly encouraged for levels >0.5µg/L. In the control group, procalcitonin was not used to guide antibiotic administration. Initial assessment in the emergency department included complete history, physical examination, measurement of body temperature, blood sampling for haematological analysis and blood chemistry, including C-reactive protein and chest radiography. Sputum and blood culture, blood gases, spirometry, bronchoscopy with BAL and consultation of an infectious disease specialist and respiratory specialist were undertaken as needed in both groups. A quality of life questionnaire and a visual scale (0% - very ill, 100% - completely healthy) were filled by all patients on admission and at follow up. Follow up: one visit 10-14 days after recruitment and one telephone follow up 4-6 months after recruitment.
Outcomes	Primary: Use of antibiotics (rate of antibiotic prescriptions in percentage and patient days, relative risk of antibiotic exposure, in patients with LRTI and AECOPD), costs of antibiotics. Secondary: Clinical and Laboratory outcomes such us quality of life indices, temperature, leucocytes, plasma c-reactive protein and procalcitonin concentrations, frequency and length of admission, need for ICU admission, mortality and rate of re-exacerbation after 6 months.

Christ-Crain 2004 (Continued)

Risk of Bias Assessment		
Bias	**Author's judgment**	**Support of judgment**
Random sequence allocation (selection bias)	**Low risk**	"We randomly assigned eligible patients either standard antimicrobial therapy (standard group) or procalcitonin-guided antimicrobial treatment (procalcitonin group) according to a computer-generated weekwise- randomisation scheme."
Allocation concealment (selection bias)	**High risk**	"We randomly assigned eligible patients either standard antimicrobial therapy (standard group) or procalcitonin-guided antimicrobial treatment (procalcitonin group) according to a computer-generated weekwise- randomisation scheme."
Blinding of participants and personel (performance bias)	**High risk**	Single blinded trial
Blinding of outcome assessment (detection bias)	**High risk**	Single blinded trial
Incomplete outcome data (attrition bias)	**Low risk**	13/243 patients were lost to follow up. The rest of the participants were successfully followed.
Selective reporting (reporting bias)	**Low risk**	Clinically relevant outcomes were reported
Other bias	**Low risk**	

Corti 2016

Reference: Corti C, Fally M, Fabricius-Bjerre A, Mortensen K, Jensen BN, Andreassen HF, Porsbjerg C, Knudsen JD, Jensen JU. Point-of-care procalcitonin test to reduce antibiotic exposure in patients hospitalized with acute exacerbation of COPD. Int J Chron Obstruct Pulmon Dis. 2016 Jun 22;11:1381-9.

Methods	Parallel quasi-randomized controlled trial. 120 patients with confirmed or suspected AECOPD were enrolled from the Acute Admissions Unit or the Pulmonary Department of Bispebjerg Hospital (Denmark) between October 2012-July 2013. Participants were followed for 30 days. The study population was based on power studies, however details are not available.
Participants	All adult patients with confirmed or suspected COPD admitted with a COPD exacerbation during weekdays and signed an informed consent.
Interventions	Participants were randomized to procalcitonin-guided antibiotic treatment or standard care at the time of admission. In the procalcitonin-guided treatment group, antibiotic use was based on procalcitonin levels at hospital admission: Levels below 0.15ng/ml were considered to indicate the absence of bacterial infection and the use of antibiotics was strongly discouraged (clinician could only overrule the algorithm after conferring with the investigators). For levels between 0.15-0.25ng/ml, antibiotics were also discouraged, unless there was a strong clinical indication of infection, such as fever, X-ray infiltrates, etc. Levels above 0.25ng/ml were considered indicative of bacterial infection and antibiotic treatment was encouraged. The duration of antibiotic administration was adjusted according to the procalcitonin levels at discharge. In the standard therapy group, antibiotic administration was based on current guidelines, according to the decision of the attending physician, who was unaware of the patient's procalcitonin levels.
Outcomes	Median duration of antibiotic exposure; antibiotic prescription rate; proportion of patients who used antibiotics for five days or more; 30 days mortality; overall re-admission rate; readmission rate due to exacerbations; composite harm endpoint consisting of death, readmission to hospital or intensive care admission within 28 days.

Corti 2016 (Continued)

Risk of Bias Assessment		
Bias	**Author's judgment**	**Support of judgment**
Random sequence allocation (selection bias)	**High risk**	"Even and uneven (concealed) digit of patient´s Danish personal identification number, not last digit (gender-fixed). Even = procalcitonin-guided, Uneven = Control."
Allocation concealment (selection bias)	**High risk**	"Even and uneven (concealed) digit of patient´s Danish personal identification number, not last digit (gender-fixed). Even = procalcitonin-guided, Uneven = Control."
Blinding of participants and personel (performance bias)	**High risk**	Non blinded
Blinding of outcome assessment (detection bias)	**Unclear risk**	Non reported
Incomplete outcome data (attrition bias)	**Unclear risk**	Data on missing participant data not presented
Selective reporting (reporting bias)	**Low risk**	Clinically relevant outcomes were reported
Other bias	**Low risk**	

Kristoffersen 2009

Reference: Kristoffersen KB, Søgaard OS, Wejse C, Black FT, Greve T, Tarp B, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission--a randomized trial. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2009; 15(5):481-7.

Methods	Parallel group, multicentre, randomized controlled trial. 223 adult patients who were admitted to the hospital with a suspicion of LRTI, including 89 patients who were admitted with an acute exacerbation of COPD, were recruited from the Department of Infectious Diseases at Aarhus University Hospital, Skejby, the Department of Medicine at Randers Hospital or the Department of Medicine at Silkeborg Hospital. The study was powered (90%) to detect a 20% reduction in antibiotic use (from 10 to 8 days), assuming a two-tailed test and a 5% level of significance. The study was not powered specifically for patients admitted with a COPD exacerbation.
Participants	Patients admitted with suspected pneumonia, with one or more clinical symptoms (cough, expectoration, dyspnoea or fever >38oC). The diagnosis of COPD was based on the past medical history of the patients and was not confirmed. Exclusion criteria: Age under 18, inability to give consent, admitted not primarily because of the respiratory tract infection, hospital acquired infections.
Interventions	Participants were randomized to either a procalcitonin-guided treatment or standard care. In the procalcitonin group, the procalcitonin test results were simply provided and all diagnostic and treatment decisions were left to the discretion of the treating clinician. Procalcitonin results were not available at the time of the initial treatment decisions and they were most frequently used to motivate continuation or discontinuation of the antibiotic treatment. Cessation was advised if procalcitonin on admission was below 0.25µg/L. Continuation of the antibiotics was encouraged for levels above 0.25µg/L and strongly encouraged for levels above 0.5µg/L. In the standard care group, procalcitonin was measured, but the results were made not available to the treating physicians and patients were treated according to regional guidelines.
Outcomes	Primary: Antibiotic use, length of stay in hospital. Secondary: Adherence to procalcitonin-guided treatment guidelines.
Notes	In 41% of cases with a serum procalcitonin of less than 0.25µg/L, physicians disregarded the treatment guidelines and continued antibiotic treatment. This was most frequently due to the clinical presentation of the patient (47%) or late arrival of the result (41%, mean time from blood sampling until procalcitonin results were available was 1.6 days).

Kristoffersen 2009 (Continued)

Risk of Bias Assessment		
Bias	**Author's judgment**	**Support of judgment**
Random sequence allocation (selection bias)	**Low risk**	"Eligible patients were randomly assigned to either PCT-guided treatment or standard care, according to a computer randomization scheme and group assignment was made by the primary investigator"
Allocation concealment (selection bias)	**Low risk**	"Eligible patients were randomly assigned to either PCT-guided treatment or standard care, according to a computer randomization scheme and group assignment was made by the primary investigator"
Blinding of participants and personel (performance bias)	**High risk**	Non blinded
Blinding of outcome assessment (detection bias)	**High risk**	Non blinded
Incomplete outcome data (attrition bias)	**Low risk**	13 patients were not included in the analyses: 3 did not have procalcitonin tested, 6 did not meet the inclusion criteria and 4 withdrew consent. The rest of patients were successfully followed until the end of the study.
Selective reporting (reporting bias)	**Low risk**	Clinically relevant outcomes were reported
Other bias	**Low risk**	

Liu 2015

Reference: Liu SS, Zhang YB. The value of serum procalcitonin level in guiding the use of antibiotic in patients with acute exacerbation of chronic obstructive pulmonary disease China: Editorial Office of Chinese Journal of Antibiotics; 2015, 6:459-63.

Methods	Quasi-randomised, parallel group, controlled trial. 108 patients who were admitted with an acute exacerbation of their COPD were recruited from the Respiratory Department of the First Affiliated Hospital of Anhui Medical University and the Anhui Provincial Chest Hospital, between February 2013 and April 2014. Power studies were not reported.
Participants	108 consecutive patients who were admitted with an acute exacerbation of COPD (COPD and COPD exacerbation diagnosed according to the local guidelines). Exclusion criteria: medullary thyroid carcinoma, history of small cell lung cancer, recent use of immunosuppressive agents, duration of the exacerbation symptoms more than 5 days at presentation, use of antibiotics within 4 weeks prior to hospital admission, consolidation in the chest x-ray, other sources of infection and severe organ dysfunction.
Interventions	Consecutive patients were divided into a procalcitonin and a conventional treatment group at the time of admission, according to the mantissa of their admission number. In the first group, serum procalcitonin levels were measured in days 1,4,7 and 10 after hospitalization, to guide antibiotic initiation and discontinuation. Antibiotics were discouraged if procalcitonin was less than 0.25μg/L, strongly discouraged if less than 0.1μg/L, encouraged if procalcitonin was more than 0.25μg/L and strongly encouraged if procalcitonin was more than 0.5μg/L. In the control group, the decision to administer antibiotics was based on clinical presentation, antibiotic treatment guidelines and clinical decision, without the use of procalcitonin. Patients were followed up at 6 months in the clinic or by a phone call.
Outcomes	Effectiveness of the procalcitonin guided antibiotic administration, Antibiotic utilization, duration of antibiotic therapy, hospitalization, medical expenses, exacerbations rate and time to next exacerbation (during 6 months follow up).

Liu 2015 (Continued)

Risk of Bias Assessment		
Bias	**Author's judgment**	**Support of judgment**
Random sequence allocation (selection bias)	**High risk**	"Patients were divided according to the mantissa of their admission number"
Allocation concealment (selection bias)	**High risk**	"Patients were divided according to the mantissa of their admission number"
Blinding of participants and personel (performance bias)	**High risk**	Non blinded
Blinding of outcome assessment (detection bias)	**High risk**	Non blinded
Incomplete outcome data (attrition bias)	**High risk (Long term only)**	18 patients were lost to long-term follow up
Selective reporting (reporting bias)	**Low risk**	No published protocol. Difficult to interpret results.
Other bias	**Unclear risk**	Power studies not reported

Nangia 2012
Reference: Nangia V, Gandhi K. Use of procalcitonin to guide the antibiotic therapy in patients with an acute exacerbation of COPD in a resource-limited setting: A case-control study: Blackwell Publishing Ltd; 2012; 64. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70822262.

Methods	Single-centre, parallel-group, randomized controlled trial. 100 patients hospitalized for acute exacerbations of COPD were enrolled.
Participants	100 consecutive adult patients who were hospitalized for an acute exacerbation of COPD. Patients should either have a known previous history of COPD or history of chronic cough for more than three months for two consecutive years (clinical definition of COPD) and who met post-bronchodilator therapy spirometric criteria according to GOLD guidelines. Exclusion criteria: Alternative explanation for the presenting signs and symptoms, vulnerable patients (i.e. those with psychiatric comorbidities), patients requiring endotracheal intubation and ventilation, within 24 hrs of admission, immunosuppressed or immunocompromised patients and patients with infiltrates on chest radiographs on hospital admission.
Interventions	Participants were randomized to procalcitonin guided antibiotic treatment or standard care. In the first group, after the first dose, antibiotics were continued only if serum procalcitonin was elevated (≥0.5µg/L), while in the control group antibiotics were given following the acceptable standards, as decided by the attending physician. Patients were monitored daily until discharge from hospital and then at 6 weeks follow up (this visit was performed by blinded investigators).
Outcomes	Primary: Total antibiotic usage during hospitalisation and up to 6 weeks. Secondary: Measures of clinical outcomes like success, self-reported functional status, lung function, steroid dosage, length of in-hospital stay and death.
Notes	No published full report available.

Nangia 2012 (Continued)

Risk of Bias Assessment		
Bias	**Author's judgment**	**Support of judgment**
Random sequence allocation (selection bias)	**Low risk**	Computer randomized study
Allocation concealment (selection bias)	**Low risk**	Computer randomized study
Blinding of participants and personel (performance bias)	**High risk**	Non blinded
Blinding of outcome assessment (detection bias)	**High risk**	Non blinded (excluding data collected in the 6 weeks visit, which was performed by blinded members of the study team)
Incomplete outcome data (attrition bias)	**Low risk**	2/50 patients were lost to follow up from the control group. All participants in the procalcitonin group were successfully followed.
Selective reporting (reporting bias)	**Low risk**	Clinically relevant outcomes were reported.
Other bias	**Unclear risk**	No power studies reported

Schuetz 2009
Reference: Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA. 2009;302(10):1059-66.

Methods	Multicentre, investigator-initiated, non-inferiority, randomized controlled trial. 1359 patients with severe lower respiratory tract infections, including 228 patients with acute exacerbation of COPD, were randomized from the emergency departments of 6 tertiary care hospitals in Switzerland, between October 2006 and March 2008. The study was powered to demonstrate non-inferiority of procalcitonin guided versus standard antibiotic prescription in the overall adverse outcomes of all patients with lower respiratory tract infections (not powered especially for COPD exacerbations).
Participants	Consecutive patients attending the emergency department with "at least 1 respiratory symptom (cough, sputum production, dyspnoea, tachypnea, pleuritic pain) plus at least 1 finding during auscultation (rales, crepitation) or 1 sign of infection (core body temperature >38oC, shivering or leukocyte count >10 000/µL or <4000/µL, independent of antibiotic pretreatment". Postbronchodilation spirometry was a prerequisite for the diagnosis of COPD (GOLD criteria). Exclusion criteria included patients with active intravenous drug use, severe immunosuppression other than corticosteroid use, life-threatening medical comorbidities leading to possible imminent death, patients with hospital-acquired pneumonia and patients with chronic infection necessitating antibiotic treatment.
Interventions	Participants were randomized to procalcitonin-guided antibiotic treatment or standard care at the time of admission. In the first group, procalcitonin levels were measured and communicated to the treating clinician along with a treatment recommendation for antibiotics which were strongly discouraged if procalcitonin was less than 0.1µg/L, discouraged if it was between 0.1-0.25µg/L, encouraged if it was between 0.25-0.5µg/L and strongly encouraged for levels >0.5µg/L. If antibiotics were withheld, hospitalized patients were re-evaluated (clinically and with procalcitonin measurement) after 6 to 24 hours. In patients with severe COPD (GOLD III or IV) and procalcitonin values of less than 0.25µg/L, the protocol could be overruled by the treating physician. In the standard therapy antibiotic use was determined by up-to-date guidelines. In COPD, antibiotic therapy was recommended for 5-10 days if the patients had either severe COPD (GOLD IV), or purulent sputum and at least one of: increased dyspnoea, increased sputum volume.
Outcomes	Primary: Noninferiority in overall adverse outcomes occurring within 30 days follow up (composite index including all-cause mortality, ICU admission for any reason, disease specific complications and recurrence of LRTI). Secondary: Antibiotic exposure, adverse effects of antibiotic treatment and length of hospital stay.

Schuetz 2009 (Continued)

Risk of Bias Assessment		
Bias	**Author's judgment**	**Support of judgment**
Random sequence allocation (selection bias)	**Low risk**	"Randomization of patients to PCT guidance or guideline enforced antibiotic therapy is based on a pre-specified computer generated randomization list and concealed by using a centralized password-secured website"
Allocation concealment (selection bias)	**Low risk**	"Randomization of patients to PCT guidance or guideline enforced antibiotic therapy is based on a pre-specified computer generated randomization list and concealed by using a centralized password-secured website"
Blinding of participants and personel (performance bias)	**High risk**	"Outcomes were assessed during the hospital stay by unblinded study physicians and by structured telephone interviews at day 30 by blinded medical students."
Blinding of outcome assessment (detection bias)	**Low risk**	"Outcomes were assessed during the hospital stay by unblinded study physicians and by structured telephone interviews at day 30 by blinded medical students."
Incomplete outcome data (attrition bias)	**Low risk**	Only 23 out of 1381 randomized patients were lost to follow up or withdrew consent.
Selective reporting (reporting bias)	**Low risk**	Clinically relevant outcomes were reported.
Other bias	**Low risk**	

Stolz 2007
Reference: Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Muller C, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest. 2007;131(1):9-19.

Methods	Single-centre, parallel, randomized controlled trial. 226 patients were enrolled from University Hospital Basel (Basel, Switzerland), between November 2003-March 2005. Participants followed up for six months. The study was powered to demonstrate and absolute reduction in the use of antibiotics among patients admitted with a COPD exacerbations, from 75% to 45%, using a procalcitonin guided strategy to decide on the administration of antibiotics.
Participants	Consecutive patients, over the age of 40, admitted with an acute exacerbation of COPD and met the GOLD post-bronchodilator spirometric diagnostic criteria, within 48 hours of the admission.
Interventions	Participants were randomized to procalcitonin-guided antibiotic treatment or standard care at the time of admission. In the procalcitonin-guided treatment group, antibiotic use was based on procalcitonin levels at hospital admission: Levels below 0.1µg/L were considered to indicate the absence of bacterial infection and the use of antibiotics was discouraged. Levels above 0.5µg/L were considered indicative of bacterial infection and antibiotic treatment was encouraged. Intermediate levels indicated possible bacterial infection, and the use of antibiotics was discouraged or encouraged respectively, based on the stability of the patient's clinical condition. In the standard therapy group, antibiotic administration was based on current guidelines, according to the decision of the attending physician, who was unaware of the patient's procalcitonin levels.
Outcomes	Antibiotic use; treatment failure at 2-3 weeks; 6-months mortality; antibiotic prescription after opposite initial decision; development of pneumonia after decision not to administer antibiotics;

Stolz 2007 (Continued)

Risk of Bias Assessment		
Bias	**Author's judgment**	**Support of judgment**
Random sequence allocation (selection bias)	**Low risk**	Independent statistician created a randomization list
Allocation concealment (selection bias)	**Low risk**	Sealed envelopes, not numbered
Blinding of participants and personel (performance bias)	**High risk**	Non blinded
Blinding of outcome assessment (detection bias)	**Low risk**	Assessed by a physician and a nurse on the study team, who were blinded to the group assignment.
Incomplete outcome data (attrition bias)	**Low risk**	18 patients were excluded secondarily for absence of COPD according to GOLD. No patient dropped out thereafter, and no patient was lost to follow up.
Selective reporting (reporting bias)	**Low risk**	Clinically relevant outcomes were reported
Other bias	**Low risk**	

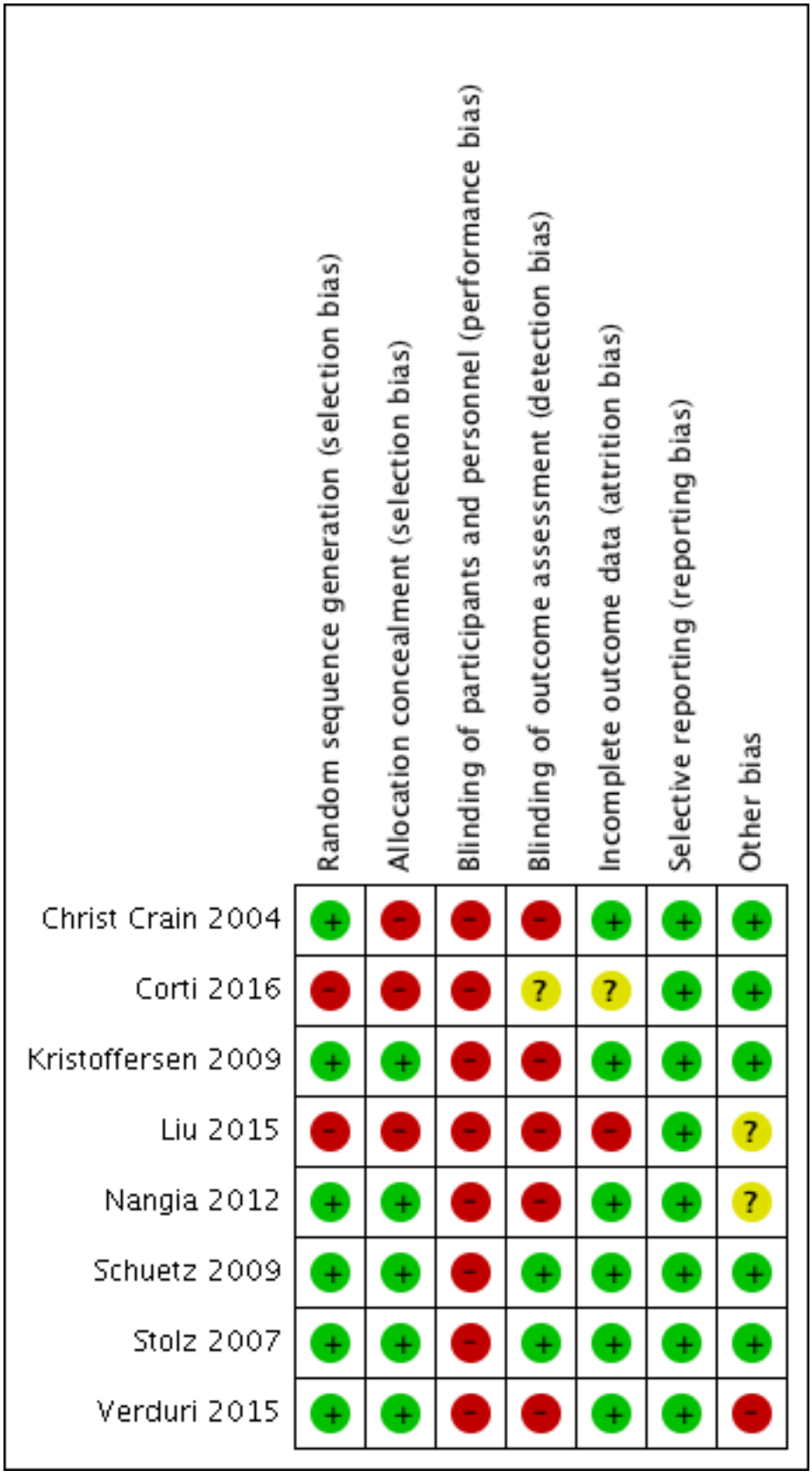
Verduri 2015
Reference: Verduri A, Luppi F, D'Amico R, Balduzzi S, Vicini R, Liverani A, et al. Antibiotic treatment of severe exacerbations of chronic obstructive pulmonary disease with procalcitonin: a randomized noninferiority trial. PloS one. 2015;10(3):e0118241.

Methods	Multicentre, non-inferiority, parallel, randomized controlled trial. 184 patients were enrolled (power studies suggested 400 patients; however, the target was not met due to very slow recruitment), from 18 hospitals in Italy. Patients were followed between January 2007 - July 2011. Sample size was calculated to show non-inferiority of procalcitonin guided versus standard antibiotic administration in the exacerbations rate within 6 months.
Participants	Male or female adults, current or former smokers, diagnosed with COPD (GOLD definition, including spirometry). Patients were hospitalized for severe exacerbation requiring antibiotic treatment (Anthonisen type 1 exacerbation) and/or characterized by respiratory failure. Exclusion criteria: Bronchial asthma, unstable concomitant disease, pregnancy and breastfeeding, clinically significant laboratory abnormalities suggestive of unstable concomitant disease, survival for 1 year unlikely and, inability to gibe written consent. Antibiotic administration before hospital admission and radiographic signs of pneumonia did not preclude eligibility.
Interventions	Participants were randomized to procalcitonin-guided antibiotic treatment or standard care. All participants assigned to the standard care group were administered antibiotic therapy for 10 days, while patients randomized to the procalcitonin group either continued antibiotics for 10 days, or stopped on day 3, depending on the procalcitonin levels (if PCT value in any of the first three days was >=0.25μg/L patients were administered antibiotics for 10 days; if maximum PCT level was between 0.1 and 0.25μg/L, antibiotic continuation was based on clinical symptoms; if PCT level was consistently less than 0.1 antibiotics were stopped on day 3).
Outcomes	The primary end point of the study was the percentage of patients with at least one exacerbation within 6 months after the index exacerbation. Secondary end points included hospital readmission, admission to the intensive care unit, change in lung function (ΔFEV1), length of hospital stay, and death from any cause.

Verduri 2015 (Continued)

Risk of Bias Assessment		
Bias	**Author's judgment**	**Support of judgment**
Random sequence allocation (selection bias)	**Low risk**	"Randomly assigned according to a 1:1 permuted block computer-generated scheme, stratified according to hospital."
Allocation concealment (selection bias)	**Low risk**	"The randomization was Web-based, and only statisticians and the website administrator knew the randomization sequence."
Blinding of participants and personel (performance bias)	**High risk**	Non blinded
Blinding of outcome assessment (detection bias)	**High risk**	Non blinded
Incomplete outcome data (attrition bias)	**Low risk**	Five patients in the procalcitonin group were not included in the analyses because they were randomized by mistake; they did not meet the inclusion criteria. All other patients were successfully followed until the end of study period.
Selective reporting (reporting bias)	**Low risk**	Preselected outcomes are reported in the manuscript.
Other bias	**High risk**	Investigators failed to recruit the target study population. Power studies suggested a population of 400 patients, but only 184 patients were finally randomized, due to slow recruitment and very strict inclusion criteria

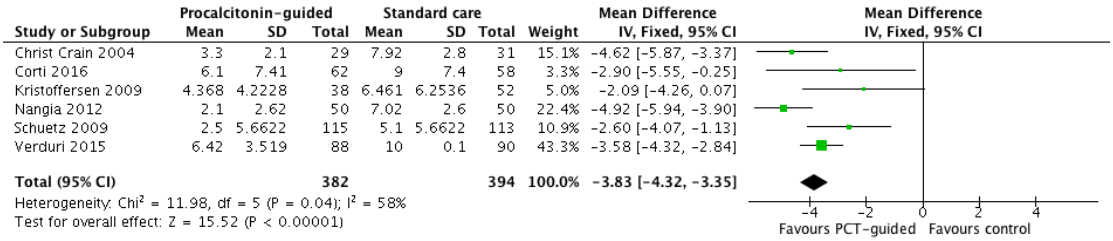
Appendix 4. Risk of bias assessment



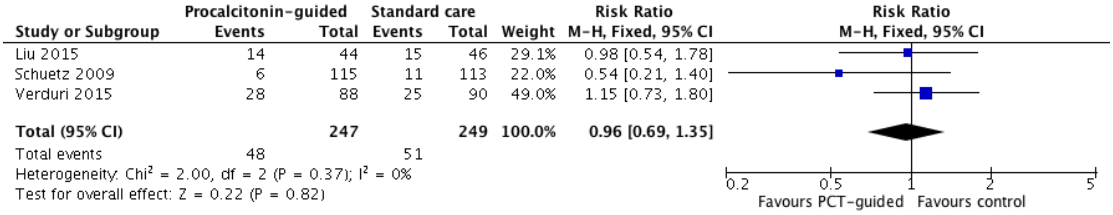
Online Figure 1. Risk of bias summary – review authors' judgements about each risk of bias domain for each included study. Attrition bias is low for all short-term outcomes of all included trials.

Appendix 5: Additional forest plots

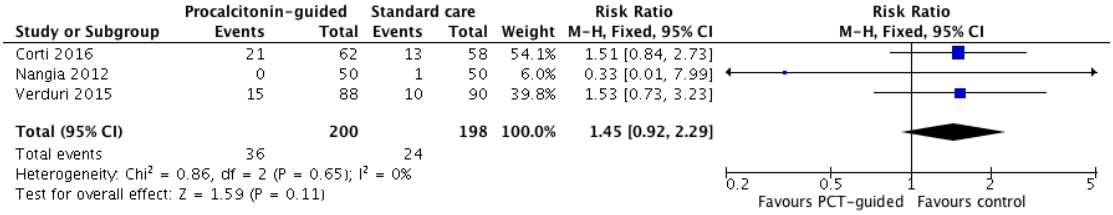
A. Antibiotic exposure for the index exacerbation: Mean duration of the antibiotic courses.



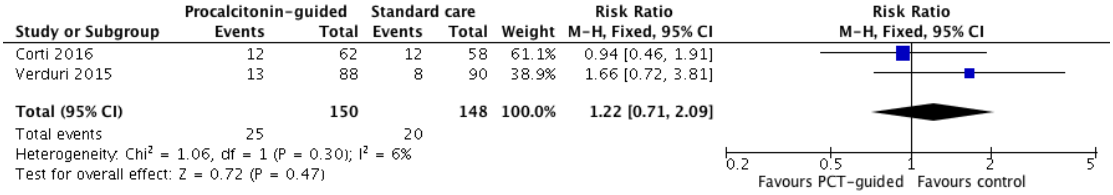
B. Re-exacerbation rate at longest follow up.



C. Re-hospitalization rate at longest follow up



D. Rate of re-hospitalization due to an exacerbation at longest follow up



Appendix 6. Evidence profile

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Procalcitonin-guided protocols	Standard care	Relative (95% CI)	Absolute (95% CI)		
Treatment failure for the index exacerbation.												
5	randomised trials	serious [1]	not serious	not serious	serious [2] OIS: 1668 participants NIM: 5%	none	73/417 (17.5%)	90/417 (21.5%)	**RR 0.81** (0.62 to 1.06)	**39 fewer per 1,000** (from 78 fewer to 12 more)	⨁⨁◯◯ LOW	CRITICAL
Lenght of hospital stay for the index exacerbation												
8	randomised trials	serious [1]	not serious	not serious	not serious OIS: 640 participants NIM: 1 day	none	526	536	**MD -0.76** (-1.95 to 0.43)	MD **0.76 days lower** (1.95 lower to 0.43 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Proportion of patients who were prescribed antibiotics on admission												
7	randomised trials	serious [1]	not serious	not serious	not serious OIS: 94 participants (25% decrease)	none	222/484 (45.9%)	406/500 (81.2%)	**RR 0.56** (0.43 to 0.73)	**348 fewer prescriptions per 1,000** (from 451 fewer to 214 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Procalcitonin-guided protocols**	**Standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Duration of the course of antibiotics												
6	randomised trials	serious [1]	not serious	not serious	not serious OIS: 244 participants (2 days less)	none	382	394	**MD -3.83** (-4.32 to -3.35)	MD **3.83 days lower** (4.32 lower to 3.35 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Exacerbation recurrence rate at longest follow-up												
3	randomised trials	serious [1]	not serious	not serious	serious [2] OIS: 1612 participants NIM: 5%	none	48/247 (19.4%)	51/249 (20.5%)	**RR 0.96** (0.69 to 1.35)	**8 fewer per 1,000** (from 63 fewer to 72 more)	⨁⨁◯◯ LOW	IMPORTANT
Re-hospitalization rate at longest follow up												
3	randomised trials	serious [1]	not serious	not serious	serious [2] OIS: 968 participants NIM: 5%	none	36/200 (18.0%)	24/198 (11.1%)	**RR 1.45** (0.92 to 2.29)	**52 more per 1,000** (from 9 fewer to 150 more)	⨁⨁◯◯ LOW	IMPORTANT
Rate of re-hospitalization due to an exacerbation at longest follow up												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Procalcitonin-guided protocols**	**Standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	serious [1]	not serious	not serious	serious [2] OIS: 1154 participants NIM: 5%	none	25/150 (16.7%)	20/148 (13.5%)	**RR 1.22** (0.71 to 2.09)	**30 more per 1,000** (from 39 fewer to 147 more)	⨁⨁◯◯ LOW	IMPORTANT
Overall mortality at longest follow up												
8	randomised trials	not serious	not serious	not serious	serious [2] OIS: 2654 participants NIM: 2%	none	23/526 (4.3%)	24/536 (4.5%)	**RR 0.99** (0.58 to 1.69)	**0 fewer deaths per 1,000** (from 18 fewer to 29 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

1. None of the included trials was blinded.

2. Not meeting optimal information size (OIS) criterion. OIS criterion was calculated accepting a Type 1 error rate a=0.05 and Power 1-β=80%. NIM: Non-inferiority margin