PART I
PROCALCITONIN-GUIDED THERAPY

CHAPTER 2

PROCALCITONIN-GUIDED THERAPY FOR THE INITIATION OF ANTIBIOTICS IN THE EMERGENCY DEPARTMENT: A SYSTEMATIC REVIEW

Yuri van der Does MD,
Pleunie P.M. Rood MD PhD,
Juanita A. Haagsma PhD,
Peter Patka MD PhD,
Eric C.M. van Gorp MD PhD,
Maarten Limper MD PhD.

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ABSTRACT

Background

Procalcitonin (PCT) is a new biomarker with a higher accuracy in the diagnosis of bacterial infections. Utilization of PCT may reduce the number of unnecessary antibiotics prescribed to patients, and consequently may decrease the rise in antibiotic resistance.

The aim of this systematic review is to determine if a PCT-guided algorithm can safely reduce the number of antibiotics prescribed to all patients with a suspected of infection in the emergency department(ED).

Methods

MEDLINE, EMBASE, Web-of-science, COCHRANE central, PubMed publisher and Google scholar were searched. Two reviewers performed the screening independently. The QUADAS 2 tool was used to assess quality.

Results

In total, 1621 articles were screened. Nine articles were included in the analysis. In the six studies on adult patients, only patients with respiratory tract infections were investigated. In these studies, a cut-off value of 0.25mcg/L was used, and PCT-guided therapy reduced the number of prescribed antibiotics significantly. Three studies were on pediatric patients, two on fever without source, and one on respiratory complaints. PCT-guided therapy did not reduce antibiotic prescription in children. PCT-guided therapy did not result in an increase in adverse events in any of the studies.

Discussion

PCT-guided therapy in the ED is only studied in subpopulations, where it was effective and safe in adult patients with respiratory tract infections, and not effective but safe nonetheless in specific pediatric populations. Nonadherence is a significant problem in prospective PCT-guided therapy studies. There is not enough evidence to use PCT-guided therapy in a general ED population.

PROSPERO Systematic review registration: CRD42015023534

INTRODUCTION

In the emergency department (ED), immediate treatment of bacterial infections is vital. Delay of administration of antibiotics is associated with morbidity and mortality in patients with severe sepsis and septic shock[1]. On the other side, the use of antibiotics in the ED, without laboratory confirmation of the definitive diagnosis, may result in an overuse of antimicrobial therapy. Consequently, adverse drug events and healthcare costs may rise and antibiotic resistance may increase[2-4]. Antibiotic resistance is a growing global problem[2,3]. Governments worldwide promote the implementation of antimicrobial stewardship programs[5]. Antimicrobial stewardship programs encourage to initiate optimal antimicrobial treatment[6]. Ideally, patients without bacterial infections would not receive antibiotics. However, in the emergency situation, it is difficult to distinguish bacterial infections from viral infections and other febrile conditions.
When a febrile patient presents at the ED, the standard diagnostic approach - besides thorough medical history taking and physical examination - consists of laboratory tests such as C-reactive protein (CRP) and leukocyte count, and different image modalities. Cultures and polymerase chain reaction (PCR) technology can be obtained in the ED, but results are not directly available and therefore not useful for ED decision-making. Procalcitonin (PCT) can be used as a biomarker for bacterial infections. Elevated levels indicate the probable presence of bacterial infections. As levels of PCT rise within approximately six hours after the start of bacterial infection and remain relatively stable, its properties are suitable for ED-application[7,8]. Compared to CRP, PCT has been shown to be more accurate in different age groups, ranging from young children with fever without source(FWS)[9,10], to geriatric patients[11]. Also, for different sites of infection, such as respiratory tract and urogenital tract[12-14], and in multiple clinical settings, including primary care, intensive care units, and in the ED, PCT is more accurate[15-17]. Although the characteristics of PCT are promising, there may be other factors that can influence the initiation of antibiotic therapy. Prospective studies give more insight in these factors, because intention-to-treat analyses can be compared with per-protocol analyses. Also, safety can be addressed in prospective studies, because unwanted undertreatment and consequent adverse events can be quantified. PCT-guided therapy is defined as initiation of antibiotic treatment using PCT measurements, usually using a suggested treatment algorithm based on the height of the PCT measurement[15]. The overall clinical value of PCT-guided therapy in the general ED population of all ages and full spectrum of febrile complaints remains to be investigated.

The aim of this systematic review is to determine if a PCT-guided algorithm can safely reduce the number of antibiotics prescribed to all patients suspected of infection in the ED.

METHODS

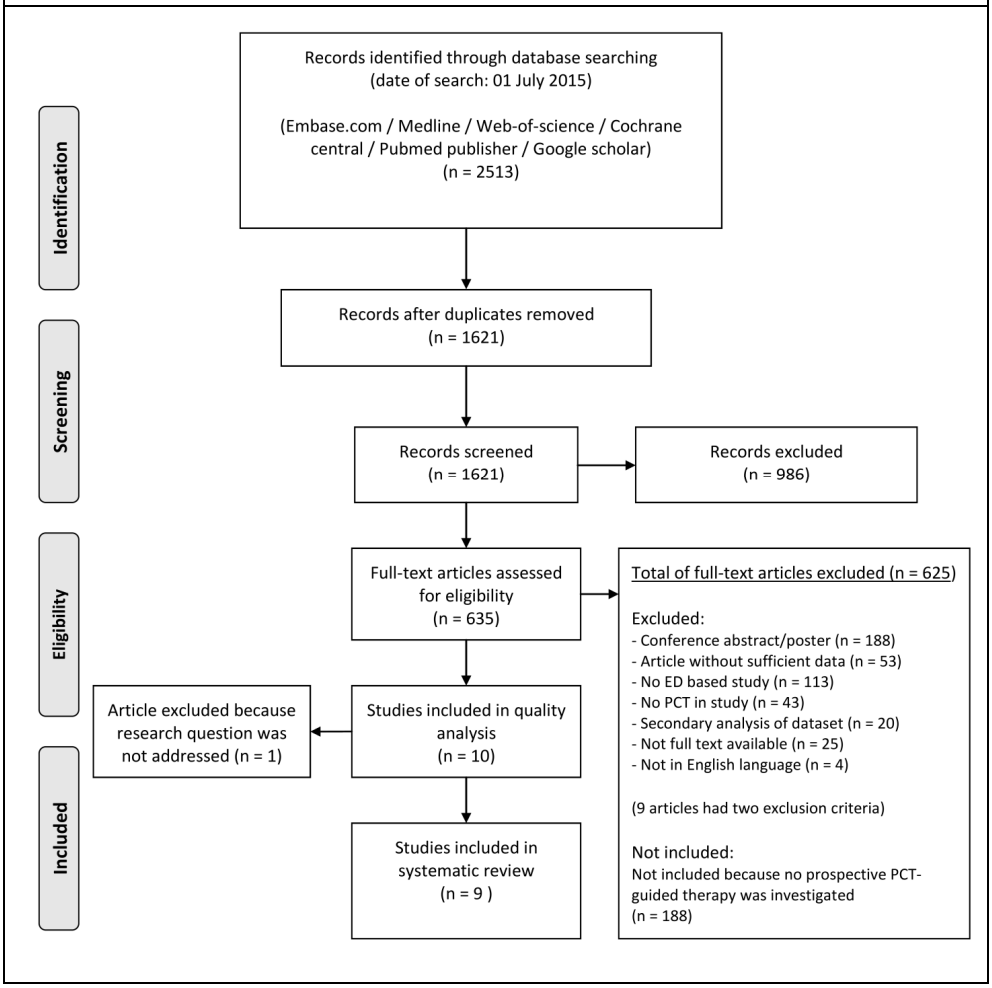
Study design

A systematic review of literature was performed according to the PRISMA guidelines[18]. The design of this systematic review is registered in the PROSPERO database[19], with registration number CRD42015023534 (http://www.crd.york.ac.uk/PROSPERO/). The primary outcome measure was the effectiveness of PCT-guided therapy in the ED, defined as reduction in the initiation of antibiotic therapy.

Search strategy

A comprehensive search, supported by a professional librarian of the Erasmus University Medical Center Rotterdam was performed. The MEDLINE, EMBASE, Web-of-science, COCHRANE central, PubMed publisher and Google scholar, containing all articles up to July 1st, 2015 were searched. The results were limited to the English language. Search terms are listed in Supplement 1. This review was restricted to articles that prospectively reported on an intervention of PCT-guided therapy in an ED setting. Outcome measures were: reduction of antibiotics (defined as number or percentage of antibiotics prescriptions), and safety of PCT-guided therapy (defined as hospital mortality, hospital or intensive care unit (ICU) admission and return visits to the ED). Studies that were not performed in the ED, i.e. in the ICU, medical or surgical wards, or primary care facilities were excluded. Furthermore, studies performed in specific departments such as burns units were excluded, as well as studies where there was no comparison between a PCT-guided therapy group and a control group of standard cares. There was no limit on age distribution or subpopulation of patients. Two authors (Y.D. and M.L.) screened titles and abstracts of the search results, and the full text of the selected articles. In case of disagreement a third reviewer (P.R.) acted as a referee. The QUADAS 2 tool[20] was used for assessing quality and bias in the selected full text studies. The QUADAS 2 tool is the recommended quality assessment tool by the Cochrane library. After positive quality assessment, data were extracted from the remaining articles as reported in supplement 2.

Figure 1. Flow diagram



RESULTS

Literature search

The search results are depicted in Figure 1. The search strategy identified 1621 individual studies. Of these studies, 635 were ED based studies that investigated PCT. A total of 198 studies investigated the accuracy of PCT on various outcomes in the ED; 188 studies did not use a prospective PCT-guided therapy algorithm and were therefore not included for further analysis. After full text screening, 10 articles remained that addressed PCT-guided therapy in a prospective setting. The overall quality of the studies was assessed using the QUADAS 2 guidelines[20].

Quality assessment

The quality assessment is described in Supplement 3, and summarized in Table 1. Although the study of Drozdov et al.[21] was eligible for inclusion in the review based on the selection criteria, it was excluded in the quality assessment. Drozdov et al.[21] did not address the initiation of antibiotics, but instead reported on a PCT-guided stopping algorithm for patients who already received antibiotic treatment for a urinary tract infection. This was not in line with the review question, and therefore the results of this study were not applicable. Stolz et al.[22] excluded patients with another explanation of dyspnea than an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and patients with psychiatric comorbidity from the study population. The exclusion of a selected part of the total population resulted in a high risk of population selection and possible effect exaggeration, because patients with medical comorbidities were excluded, and patients with possible lower therapy adherence may have been excluded. There was an unclear risk of bias in patient selection in six studies. Lacroix et al.10 used temperature ≥38.0°C as an inclusion criterion. Patients were also included if parents had measured a temperature of ≥38.0°C at home. Lacroix et al.10 reported a low adherence to the combined Lab-score, a prediction model containing a PCT value. No reasons for nonadherence were reported. This raised concerns on the applicability of the results of this study. Furthermore, the authors reported a missed inclusion rate of 75%, but gave no description of individual reasons. This may have resulted in a selection bias. Three studies[9,13,23] used an envelope as randomization method. This method is associated with an increased risk of selection bias, because allocation concealment can be deciphered by holding envelopes against a lightsource[24]. Christ-Crain et al.13 excluded 47 of a total of 597 eligible patients because of “other reasons”. Long et al.[25] excluded 115 patients without specifying the reason of exclusion. The index test description had an unclear risk of bias in two studies. Baer et al.[26] did not report a final diagnosis of the febrile episode. It is not possible to check if the antibiotics were indicated retrospectively. Manzano et al.[9] did not give an antibiotic treatment advice. A concrete cut-off value for PCT with a treatment suggestion could have influenced the results of this study.

Main study results

The selected articles are shown in Table 2. Nine randomized controlled trials met the selection criteria listed in figure 1 and the QUADAS 2 criteria in Table 1. These studies consisted of two multicenter trials [17, 26] and seven single center studies[9,10,13,14,22,23,25]. Six studies[10,13,14,17,22,26] were conducted in Switzerland, five of these[13,14,17,22,26] in the university hospital of Basel. The remaining studies were performed in China[23,25] and Canada[9].

Table 1. QUADAS 2

First author, year, country	Risk of bias				Concerns on applicability		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Baer 2013, Switzerland	Low	Unclear	Unclear	Low	Low	Unclear	Low
Christ-Crain 2004, Switzerland	Unclear	Low	Low	Low	Low	Low	Low
Christ-Crain 2006, Switzerland	Unclear	Low	Low	Low	Low	Low	Low
Drozdov 2015, Switzerland	Unclear	Low	Low	Low	High	High	Low
Lacroix 2014, Switzerland	Unclear	Unclear	Low	High	Low	Unclear	Low
Long 2011, China	Unclear	Low	Low	Low	Low	Low	Low
Manzano 2010, Canada	Unclear	Unclear	Low	Low	Unclear	Low	Low
Schuetz 2009, Switzerland	Low	Low	Low	Low	Low	Low	Low
Stolz 2007, Switzerland	High	Low	Low	High	Low	Low	Low
Tang 2013, China	Unclear	Low	Low	Low	Low	Low	Low

Study populations

Sample sizes of the studies varied widely, ranging between 15623 and 135917 patients, with six studies[9,10,13,14,22,26] having sample sizes between 200 and 400 patients. Three studies reported on pediatric patient[s9,10,26], of which two[9,10] reported on newborns and infants with FWS, and one on pediatric patients with respiratory tract infections[26].

Six studies reported on adult patients with subcategories of respiratory complaints: community acquired pneumonia[14,25], acute lower respiratory tract infections[13,17], AECOPD22 and exacerbation of asthma23. The age of patients ranged from newborn children between seven days and three months of age[10] to septuagenarians[17]. The majority of the participants were males (>50% men in six[10,13,14,17,25,26] out of the nine studies). One study[9] did not report gender. None of the studies reported ethnicity.

Selection criteria studies

Inclusion criteria of the studies on lower respiratory tract infections[13,14,17,25,26] included body temperature of ≥38°C (100.4° F), combined with at least one symptom of infection, i.e. cough, sputum production or dyspnea, and one clinical sign, i.e. abnormal breath sounds or leukocytosis. The criterion for suspected community acquired pneumonia was an infiltrate on a chest X-ray. Inclusion criteria on asthma and COPD were based on reaction to beta-2-agonist use[22,23]. One study used temperature measured at home as inclusion criterion[26]. Two pediatric studies on FWS[9,10] included a measured body temperature of ≥38°C, without the presence of a suspected cause of fever after history and physical examination[10], and the need for blood and urinary analysis[9]. Eight studies[9,10,13,14,17,22,25,26] reported immunosuppression as an exclusion criterion. This criterion was not uniformly defined. Some studies gave examples of specific conditions, i.e. HIV infection with low CD4+ count[13,26], neutropenic patients[13,26], active tuberculosis[13,14,25] and cystic fibrosis1[3,14,22,25,26]. Four studies[9,10,23,25] excluded patients with current antibiotics use or within 14 days of ED presentation. Schuetz et al.[17] excluded intravenous drug users. Stolz et al.[22] excluded 'vulnerable patients': patients with psychiatric diagnoses, which were not defined.

PCT cut-off values

Seven studies[13,14,17,22,23,25,26] used a cut-off of 0.25 mcg/L to suggest or encourage the initiation of antibiotics. Two pediatric studies did not use a continuous cut-off scale. Lacroix et al.[10] used PCT as part of the Lab-score, a decision rule that combined a semi-quantitative PCT result with a semi-quantitative CRP value and urinary dipstick outcome. The Lab-score is a severity index scale, and the outcome had no directly suggested treatment consequences. Manzano et al.[9] studied PCT prospectively without treatment algorithm, only the PCT result was available, without treatment advice.

Overruling of PCT-guided therapy protocol and nonadherence

Two studies[17,26] described predefined criteria for overruling PCT-guided therapy. These criteria comprised of life threatening illness, defined as respiratory or hemodynamic instability. Schuetz et al.[17] also included a positive screening test for Legionella pneumophilia as criterion. Four[10,13,14,17] studies reported physician nonadherence, ranging from 6% to 20%. In the studies with predefined criteria, Schuetz[17] reported that 9% of the patients were excluded without meeting the nonadherence criteria. Baer et al.[26] only mentioned predefined criteria, and did not report the number of physician nonadherence, nor protocol violations.

Antibiotics reduction

PCT-guided therapy resulted in a significant reduction of antibiotics in all studies in adult patients[13,14,17,22,23,25] (Table 3). In the three pediatric studies, no significant reduction in antibiotics was noted[9,10,26]. No study reported an increase in initiation of antibiotics. All results were from the intention-to-treat analyses.

Patient related outcomes

Five studies[13,14,17,22,23] reported mortality and ICU admission. Death rates varied between 3%13 to 13%14. ICU admittance or mechanical ventilation was required for 5%13 to 14%14 of patients. No studies reported a significant difference between groups for death rates or ICU admission. Seven studies[9,10,13,14,17,22,26] reported hospital admissions. The admission rate ranged from 26%[9] to 97%[14.] No study found a significant difference between hospital admissions. Five studies[13,14,17,22,26] reported length of hospital stay; none found significant differences between groups. One study[25] included patients who were sent home from the ED, and one study[23] did not report a hospital admission number.

Table 2: Study characteristics

First author, year, country	Study population *	Age distribution in years	Gender distribution (male)	Inclusion criteria	Exclusion criteria	PCT cut-off value used	Overruling of algorithm
Baer 2013, Switzerland	337 patients	PCT group: median [IQR] 2.7 [1.1 - 5.2]. Control group: 2.9 [1.2 - 5.7].	PCT group: 98 (58%). Control group: 98 (58%).	Pediatric patients, age 1 month - 18 years, presenting with LRTI, defined as T ≥38°C (measured at home or hospital), with one symptom (cough, sputum production, pleuritic pain, poor feeding) and one clinical sign (tachypnea, dyspnea, wheezing, late inspiratory crackles, bronchial breathing, pleural rub).	Unwillingness or unable to provide written informed consent by patients and care-takers, severe immune suppression (HIV with <15% CD4 count, immunosuppressive treatment, neutropenia (<1000 x 10^9/L)), cystic fibrosis, acute croup, hospital stay within previous 14 days, other severe infection.	Antibiotics definitely (> 0.5 mcg/L), probably (0.26–0.5 mcg/L), probably not (0.1–0.25 mcg/L), and definitely not (0.1 mcg/L).	In patients with life threatening infections, defined as severe co-morbidity, emerging ICU need during initial follow-up, or hemodynamic or respiratory instability.
Christ-Crain 2004, Switzerland	243 patients	PCT group (mean ± SD): 62.8 ± 19.8. Control group: 65.3 ± 17.3 .	PCT group: 67 (54%). Control group 61 (51%).	Adult patients with suspected LRTI, defined as community acquired pneumonia, COPD, asthma, acute bronchitis.	Severely immunocompromised patients i.e. HIV infection with CD4 count <200cells/mL, neutropenic patients, stemcell transplant recipients, cystic fibrosis, active tuberculosis, hospital acquired pneumonia on ED presentation.	Antibiotics discouraged (0.1-0.25mcg/L), suggested (0.25-0.5mcg/L), strongly recommended (>0.5mcg/L).	Not reported.
Christ-Crain 2006, Switzerland	302 patients	PCT group (mean ± SD): 70 ± 17. Control group: 70 ± 17.	PCT group: 94 (62%). Control group 93 (62%).	Adult patients with suspected CAP, defined as infiltrate on chest X-ray, and one of more symptoms or signs: cough, sputum production, dyspnea, temp ≥38.0°C and up, abnormal breath sounds, rales on auscultation, leukocytosis 10 x 10^9/L and up, or less than 4 x 10^9/L.	Cystic fibrosis, active pulmonary tuberculosis, hospital acquired pneumonia on ED presentation., severely immunocompromised patients (not defined).	Antibiotics strongly discouraged (<0.1 mcg/L), discouraged (0.1-0.25mcg/L), encouraged (0.25-0.5mcg/L), strongly encouraged (>0.5mcg/L).	Not reported.
Lacroix 2014, Switzerland	271 patients*	Age in months. PCT group (median [IQR]) 4.8 [1.7 - 10.4]. Control group 3.4 [1.5 - 10.4].	PCT group: 65 (50%). Control group 71 (51%).	Pediatric patients between 7 days and 3 years old with fever without source (FWS): Temperature ≥38°C, with no identified source of infection after thorough history and physical examination. Parental informed consent.	Congenital or acquired immunodeficiency syndromes, antibiotic administration <48h of presentation, fever >7 days.	Lab score: PCT <0.5ng/mL (0), 0.5 - 1.99 ng/mL (2), ≥2 ng/mL (4). In combination with CRP value based score, and Urinary dipstick based score. A Lab score of ≥3 was used as marker for severe bacterial illness.	No algorithm of antibiotic treatment advice reported. Therefore, overruling is also not reported.
Long 2011, China	162 patients*	PCT group (mean ± SD): 44 ± 16. Control group: 47 ± 19.	PCT group: 46 (60%). Control group 49 (62%).	Adult patients with suspected CAP, defined as infiltrate on chest X-ray, and one of more symptoms or signs: fever, cough, purulent sputum, focal chest signs, dyspnea or pleuritic pain. Outpatient treatment.	Pregnancy, commencement of antibiotic therapy >48h before enrolment, systemic immune deficiency, withholding life-support and active tuberculosis.	Antibiotics strongly discouraged (<0.1 mcg/L), discouraged (0.1-0.25mcg/L), encouraged (0.25-0.5mcg/L), strongly encouraged (>0.5mcg/L).	Not reported.
Manzano 2010, Canada	384 patients*	Age in months. PCT group(mean ± SD): 12 ± 8. Control group: 12 ± 8.	Not reported	Pediatric patients, age between 1 and 36 months, a history of rectal temperature ≥38.0°C, no identified source of infection, indication for blood and urine analysis.	Acquired or congenital immunodeficiency, current antibiotics use.	For intention-to-treat analysis no cut-off defined. Semiquantitative test: <0.5ng/mL, 0.5 ng/mL or higher, 2 ng/mL or higher, 10ng/mL or higher. Per protocol analysis with prophylactic antibiotics with PCT level >0.5ng/mL or higher.	No algorithm of antibiotic treatment advice reported. Therefore, overruling is also not reported.
Schuetz 2009, Switzerland	1359 patients*	PCT group: median [IQR] 74 [59-82]. Control group: 72 [59-82].	PCT group: 402 (60%). Control group 380 (55%).	Adult patients with suspected LRTI, defined as at least one respiratory symptom (cough, sputum, dyspnea, tachypnea, pleuritic pain), plus either rales or crepitation on auscultation, or temperature >38.0°C, shivering, leukocytosis.	Inability to give informed consent, active intravenous drug use, severe immunosuppression other than corticosteroid use, life-threatening comorbidity, community acquired pneumonia.	Antibiotics strongly discouraged (<0.1 mcg/L), discouraged (0.1-0.25mcg/L), encouraged (0.25-0.5mcg/L), strongly encouraged (>0.5mcg/L).	Patients in need of ICU admission, respiratory or hemodynamic instability, positive Ag test for Legionella pneumophila, or after consulting with the study center.
Stolz 2007, Switzerland	208 patients*	PCT group: median [IQR] 69.5 [65-77]. Control group: 69.5 [64.8-79].	PCT group: 50 (49%). Control group 44 (42%).	Adult patients with exacerbation of COPD, who met post bronchodilator therapy spirometric criteria according to GOLD guidelines, within 48h of ED admission.	Patients with other explanations for presenting symptoms other than COPD, and "vulnerable patients" ie patients with psychiatric diagnoses (not specified). Immunosupression, asthma, cystic fibrosism presence of infiltrates on chest X-ray on hospital admission.	Antibiotics strongly discouraged (<0.1 mcg/L), discouraged (0.1-0.25mcg/L), encouraged (0.25-0.5mcg/L), strongly encouraged (>0.5mcg/L).	Not reported.
Tang 2013, China	156 patients*	PCT group (mean ± SD): 54 ± 14. Control group: 55 ± 15.	PCT group: 64 (50%). Control group 59 (47%).	Adult patients with suspected exacerbation of asthma, with any or all GINA asthma guidelines criteria: dyspnea, wheeze, acute cough, increased work of breathing, increased beta2 agonist use, O2 saturation <95%, peakflow<80% of known best.	Treatment with antibiotics within two weeks of recruitment, non-respiratory bacterial infection, chest X-ray confirmed pneumonia, other chronic respiratory disease, severe organ dysfunction.	Antibiotics strongly discouraged (<0.1 mcg/L), discouraged (0.1-0.25mcg/L), encouraged (0.25-0.5mcg/L), strongly encouraged (>0.5mcg/L).	Not reported.

* Studies reported both a number of randomised and number of analyzed patients. Number of analyzed patients is reported. For number of ommited patients in analysis, see table 1. CAP: Community acquired pneumonia. COPD: Chronic obstructive pulmonary disease. ED: Emergency department. GINA: Global initiative for asthma. GOLD: Global initiative for chronic obstructive lung disease. HIV: Human immunodeficiency virus. ICU: Intensive care unit. IQR: Inter quartile range. LRTI: Lower respiratory tract infection. PCT: Procalcitonin. SD: Standard deviation.

Table 3: Study outcomes

First author, year, country	Antibiotics reduction	Hospital admission	Length of hospital stay	ICU admission	ICU length of stay	Return visits to ED	Mortality	Combined safety endpoint	Physician non-adherence with PCT advice
Baer 2013, Switzerland	PCT group 104 (62%), control group 93 (56%). Reduction 6% (95%CI -5% - 16%) in all patients. 28% (95%CI 12% - 43%) in non-CAP patients, -8% (95%CI - 19% - 4%) in CAP patients.	PCT group 104 (62%) Control group 100 (60%) Reduction 2% (95%CI -8% - 12%).	PCT group (days, median,[IQR]) 2.6 (2 [0-4]) Control group 2.7 (2 [0-5]) Reduction: -0.1 (95%CI -0.8 - 0.5).	Not reported separately.	Not reported	Not reported.	None reported.	Defined as hospital readmission, ICU admission, complications or death, complications of LRTI, disease specific failure: PCT group 38 (23%) Control group 33(20%) Reduction 2% (95%CI -5 - 11%)	Not reported.
Christ-Crain 2004, Switzerland	Antibiotics in 154 (63%) patients. PCT group 55 (44%). Control group 99 (83%). P<0.001.	PCT group 101 (81%). Control group 88 (74%). P=0.16.	PCT group (days, mean ± SD) 13.7 ± 7.3. Control group 10.8 ± 7.0. P=0.25.	PCT group 6 (5%). Control group 5 (4%). P=0.71.	Not reported	Not reported.	PCT group 4 (3%). Control group 4 (3%). P=0.95	Not reported.	In 9 patients (7%) antibiotics when PCT was <0.1. In 13 patients (10%) antibiotics when PCT was <0.25. After re-evaluation after 6-24h: of a total of 29 patients in PCT group, 10 received antibiotics, 5 because of elevated PCT levels, 5 because of physician decision.
Christ-Crain 2006, Switzerland	PCT group: 128 (85%). Control group 149 (99%). P<0.001. HR 3.2 (95%CI 2.5 - 4.2).	PCT group 146 (97%). Control group 146 (97%). P=1.0.	PCT group (days, mean ± SD) 12.0 ± 9.1. Control group 13.0 ± 9.0. P=0.35.	PCT group 20 (13%). Control group 21 (14%). P=0.87.	Not reported	Treatment failure (after 6 weeks): 51 patients (17%) PCT group 24 (16%). Control group 27 (18%). P=0.65.	PCT group 18 (12%). Control group 20 (13%). P=0.73.	Not reported.	In 1 patient (0%) antibiotics when PCT was <0.1. (endstage pulmonary fibrosis). In 19 patients (6%) antibiotics when PCT was <0.25. (6 severe COPD, 2 endstage pulmonary fibrosis, 11 other severe comorbidities).
Lacroix 2014, Switzerland	PCT group 54 (41%), control group 42 (42%). P = 1.000.	PCT group 44 (34%). Control group 50 (36%). P = 0.810.	Not reported.	Not reported.	Not reported	Not reported.	Not reported.	Not reported.	In 14 (11%) cases, patients received antibiotics despite the low Lab score. No patients with high Lab scores were witheld antibiotics.
Long 2011, China	PCT group: 69 (85%). Control group 79 (98%). P=0.004. HR 3.2 (95%CI 2.5 - 4.2).	None.	Not applicable.	Not applicable.	Not applicable	Treatment failure (after 4 weeks): 21 patients (13%) PCT group 12 (15%). Control group 9 (11%). No significant difference.	None reported.	Not reported.	Not reported.
Manzano 2010, Canada	PCT group: 48 (25%). Control group: 54 (28%). Risk difference -3 (95%CI -2 to 6).	PCT group: 50 (26%). Control group: 48 (25%). Risk difference 1 (95%CI -8 - 10).	Not reported.	Not reported.	Not reported	Not reported	Not reported.	Not reported.	No antibiotic treatment advice was given.
Schuetz 2009, Switzerland	PCT group 506 (75%), control group 603 (88%). Relative rate difference -12.2 (95%CI -16.3 to -8.1).	PCT group: 628 (93%). Control group: 629 (91%).	PCT group in days: mean (median [IQR]) 9.4 (8 [4-12]) Control group 9.2 (8 [4-12]) Reduction: 1.8 (95%CI -6.9 - 11.0).	PCT group 43 (6%). Control group 60 (9%). Risk difference -2.3 (95%CI -5.2 to 0.4).	Not reported	Recurrence of LRTI/rehospitalisation PCT group 25 (4%). Control group 45 (7%). Risk difference -2.8 (95%CI -5.1 to -0.4).	PCT group 34 (5%). Control group 33 (5%). Risk difference 0.3 (95%CI -2.1 to 2.5).	Death, ICU admission, recurrence of LRTI/rehospitalisation <30 days. PCT group 103 (15%). Control group 130 (19%). Risk difference -3.5 (95%CI -7.6 to 0.4)	In 132 (20%) patients, the PCT algorithm was overruled, of which 62 (9%) were in violation of predefined protocol.
Stolz 2007, Switzerland	PCT group 41 (40%), control group 76 (72%). P <0.0001.	Hospital admission 24h or longer. PCT group: 80 (78%). Control group: 82 (77%). P = 0.852.	PCT group in days: (median [IQR]) 9 [1-15]. Control group 10 [1-15]. P = 0.960.	PCT group 8 (8%). Control group 11 (10%). P = 0.526.	PCT group in days: (mean ± SD) 3.3 ± 2.7. Control group 3.7 ± 2.1. P = 0.351.	Recurrence of ECOPD within 6 months: PCT group 44 (43%). Control group 43 (40%). P = 0.607.	Any cause mortality within 6 months: PCT group 5 (5%). Control group 9 (9%). P = 0.409.	Not reported.	Not reported.
Tang 2013, China	PCT group 59 (46%), control group 95 (75%). P <0.01.	Not reported.	Not reported.	Mechanical ventilation treatment: PCT group 8 (6%). Control group 9 (7%). P = 0.821.	Not reported	Secondary ED visit within 6 weeks. PCT group 8 (6%). Control group 13 (10%) p < 0.05.	PCT group 1. Control group 2. Excluded from further analysis.	Not reported.	Not reported.

CAP: Community acquired pneumonia. CI: Confidence interval. COPD: Chronic obstructive pulmonary disease. ECOPD: Exacerbation of chronic obstructive pulmonary disease. HR: Hazard ratio. ICU: Intensive care unit. IQR: Inter quartile range. LRTI: Lower respiratory tract infection. PCT: Procalcitonin. SD: Standard deviation.

DISCUSSION

Findings

The results of our study show that PCT-guided therapy is only studied prospectively in distinct ED patient populations, adults with respiratory complaints[13,14,17,22,23,25], and in young infants with respiratory complaints[26] and FWS[9,10]. In the studies on adult patients with respiratory complaints, PCT-guided therapy reduced antibiotic prescriptions. In the pediatric subgroups, there was no reduction. In all included studies, there was no undertreatment and there was no increase in adverse events in the intervention group. This suggests that PCT-guided therapy is safe in the patients of these distinct ED populations. PCT-guided therapy has been shown to reduce antibiotic prescriptions in adult patients with respiratory complaints in various clinical settings. In primary care, reduction of antibiotics was 72%[16]. One hospital based study on patients with lower respiratory tract infections did not find a significant reduction in antibiotic prescriptions, due to a reported protocol nonadherence of 41%. The per-protocol did result in a 25% reduction of antibiotics based on a single PCT value27. PCT studies in the ICU mainly focus on stopping antibiotics instead of starting. Several ICU studies show a reduction in duration of antibiotic treatment using PCT-guided therapy[15,28,29.] The most interesting finding was that nonadherence to PCT-guided algorithms was present in several included studies. Lacroix et al.[10] reported that the use of a PCT-guided algorithm, included in the Lab-score, did not result in a reduction in antibiotics in practice. However, per-protocol analysis showed that the algorithm would result in reduction, had it been followed. This illustrates the point that physicians do not always follow the advice of a PCT-guided therapy. This is confirmed by the nonadherence to the PCT-guided therapy algorithms several of the other included studies[10,13,14,17.] Nonadherence is only visible in prospective studies; because, in contrary to observational studies, randomized controlled trials report an intention-to-treat analysis, which includes the physician factor in the results. Prospective PCT-guided therapy studies in other clinical settings also show nonadherence. Briel et al.[16] reported a nonadherence rate of 15% in primary care. Kristoffersen et al.[27] reported a 41% nonadherence in a hospital based setting. In the ICU setting, he PRORATA trial[15] had a protocol nonadherence for stopping antibiotic therapy based on a PCT-guided algorithm of 53%, a recent ICU study reported a 56% nonadherence rate when physicians were asked to stop antibiotics within 24 hours after initiation[29]. PCT-guided therapy is accompanied by protocol nonadherence, and this finding is consistent in multiple clinical settings. We speculate that individual clinical experience is the cause of the lower reduction of antibiotics in intention-to-treat results. This may be caused by the lack of understanding of the factors that influence PCT levels[30]. The results of this systematic review cannot be extrapolated to a general ED population, because the studies included in this systematic review focused on specific subpopu-

lations of patients with respiratory complaints. The study aim was to investigate the value of PCT-guided therapy for all patients in the ED. For this reason, we did not limit the results on specific populations, but included all ED studies from young children to elderly patients. However, our search results only yielded specific subpopulations. We can conclude that PCT-guided therapy is not studied in a wide enough population to use PCT as a standard biomarker for bacterial infections in the ED. The overall quality assessment indicated a low risk on bias in the selected articles. The study by Drozdov et al.[21] did not give information on antibiotic initiation and was therefore excluded. Two studies had a high risk on bias. Stolz et al.[22] excluded patients with possible other explanations for dyspnea than acute exacerbation of COPD (AECOPD). Also, patients with psychiatric comorbidities were excluded. This may have resulted in an exaggeration of the effect of PCT-guided therapy, because merely a part of the total population of patients with AECOPD was analyzed. In the study by Lacroix et al.[10], patient selection issues were noted as well. These studies were included, because the studies both used a PCT-guided algorithm and investigated reduction of antibiotics, and therefore give insight in the effectiveness of PCT-guided therapy in the ED. Because of the high risk of selection bias in these studies, the results cannot be generalized to either the general population of adult ED patients with AECOPD, or to the general population of pediatric ED patients with FWS.

Limitations

It was not possible to pool the data of the nine included studies, because we found insufficient studies with comparable study populations. A pooling of the results of PCT-guided therapy in adults may have resulted in a reduction of antibiotics in adult patients, and to no effect in pediatric patients. However, because of the highly selective populations of the selected studies, these outcomes would not have had added value. This review was performed in 2015. There are several studies being performed at the time of writing, which study PCT-guided therapy, for instance the NeoPInS trial[31]. These results are not available at this moment, but may further clarify the value of PCT-guided therapy. The review is primarily intended for emergency physicians. Therefore, only investigated ED based studies were included. The ED is a unique clinical setting, which has specific problems such as the diagnostic uncertainty at a time when emergency treatment has to be initiated. Hence, the choice for this setting reduces the generalizability of the results to other settings. Five studies[10,13,14,17,23,25] reported on funding. Investigators of three of these studies received funding from the manufacturer of the PCT assay[10,13,17]. The authors of three studies[13,14,17] reported receiving payments for speaking engagements, lecture fees and consultancy work for the manufacturer of the PCT assay. Conflicts of interest might raise concern in the appreciation of the results[32].

CONCLUSION

PCT-guided therapy is a valuable strategy in antimicrobial stewardship, and can theoretically reduce the number of unnecessary antibiotics prescribed to ED patients. However, protocol nonadherence is a significant problem in the prospective PCT-guided therapy studies. In adult patients with suspected respiratory infections, PCT-guided therapy may reduce antibiotic prescriptions, without increasing adverse events. However, physician judgment is still crucial and cannot be replaced by biomarkers in these patient populations based on the available evidence. In pediatric patients, PCT-guided therapy was ineffective, because nonadherence to the PCT-guided algorithm reverses the theoretical reduction in antibiotics. PCT-guided therapy can only become standard therapy in the ED when it is validated in a representative sample. Also, additional evidence on the physiologic properties of PCT may result in more confidence in PCT-guided algorithms.

Acknowledgements:
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REFERENCES

1. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165-228.
2. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2003;36:1433-7.
3. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance-the need for global solutions. The Lancet Infectious diseases 2013;13:1057-98.
4. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 2014;14:742-50.
5. Spellberg B, Bartlett J, Wunderink R, Gilbert DN. Novel approaches are needed to develop tomorrow's antibacterial therapies. American journal of respiratory and critical care medicine 2015;191:135-40.
6. Dellit TH, Owens RC, McGowan JE, Jr., et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77.
7. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993;341:515-8.
8. Soni NJ, Samson DJ, Galaydick JL, et al. Procalcitonin-guided antibiotic therapy: a systematic review and meta-analysis. Journal of hospital medicine 2013;8:530-40.
9. Manzano S, Bailey B, Girodias JB, Galetto-Lacour A, Cousineau J, Delvin E. Impact of procalcitonin on the management of children aged 1 to 36 months presenting with fever without source: A randomized controlled trial. Am J Emerg Med 2010;28:647-53.
10. Lacroix L, Manzano S, Vandertuin L, Hugon F, Galetto-Lacour A, Gervaix A. Impact of the lab-score on antibiotic prescription rate in children with fever without source: A randomized controlled trial. PLoS ONE 2014;9.
11. Lai CC, Chen SY, Wang CY, et al. Diagnostic value of procalcitonin for bacterial infection in elderly patients in the emergency department. J Am Geriatr Soc 2010;58:518-22.
12. Bressan S, Andreola B, Zucchetta P, et al. Procalcitonin as a predictor of renal scarring in infants and young children. Pediatr Nephrol 2009;24:1199-204.
13. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet 2004;363:600-7.
14. Christ-Crain M, Stolz D, Bingisser R. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2006;174(1):84-93 2006.
15. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463-74.
16. Briel M, Schuetz P, Mueller B, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. Archives of internal medicine 2008;168:2000-7; discussion 7-8.
17. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: The ProHOSP randomized controlled trial. J Am Med Assoc 2009;302:1059-66.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9, W64.
19. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L. An international registry of systematic-review protocols. Lancet 2011;377:108-9.
20. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-36.
21. Drozdov D, Schwarz S, Kutz A, et al. Procalcitonin and pyuria-based algorithm reduces antibiotic use in urinary tract infections: A randomized controlled trial. BMC Med 2015;13.
22. Stolz D, Christ-Grain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 2007;131:9-19.

23. Tang J, Long W, Yan L, et al. Procalcitonin guided antibiotic therapy of acute exacerbations of asthma: A randomized controlled trial. BMC Infect Dis 2013;13.
24. Schulz KF. Subverting randomization in controlled trials. J Am Med Assoc 1995;274:1456-8.
25. Long W, Deng X, Zhang Y, Lu G, Xie J, Tang J. Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia. Respirology 2011;16:819-24.
26. Baer G, Baumann P, Buettcher M, et al. Procalcitonin Guidance to Reduce Antibiotic Treatment of Lower Respiratory Tract Infection in Children and Adolescents (ProPAED): A Randomized Controlled Trial. PLoS ONE 2013;8.
27. Kristoffersen KB, Sogaard OS, Wejse C, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission--a randomized trial. Clin Microbiol Infect 2009;15:481-7.
28. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J Respir Crit Care Med 2008;177:498-505.
29. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. The Lancet Infectious diseases 2016;16:819-27.
30. Gilbert D. Serum procalcitonin levels: comment on “Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in ‘real life’”. Arch Intern Med 2012;172:722-3.
31. Stocker M, Hop WC, van Rossum AM. Neonatal Procalcitonin Intervention Study (NeoPInS): Effect of Procalcitonin-guided decision making on duration of antibiotic therapy in suspected neonatal early-on set sepsis: A multi-centre randomized superiority and non-inferiority Intervention Study. BMC Pediatr 2010;10:89.
32. Friedman LS, Richter ED. Relationship between conflicts of interest and research results. J Gen Intern Med 2004;19:51-6.

Supplement 1. Search terms per database

Embase.com

(procalcitonin/exp OR (procalcitonin* OR (calcitonin* NEAR/3 (precursor* OR prohormone*)) OR (pct NEAR/3 (value* OR level* OR marker* OR biomarker* OR blood* OR sample* OR collect*))):ab,ti) AND ('emergency treatment'/exp OR emergency/exp OR 'emergency nursing'/exp OR 'emergency health service'/exp OR 'emergency ward'/exp OR 'emergency medicine'/exp OR traumatology/exp OR 'multiple trauma'/exp OR (emergenc* OR 'acute care' OR trauma* OR resuscitat* OR ed)) AND ([english]/lim)

Medline (OvidSP)

((Calcitonin/ AND Protein Precursors/) OR (procalcitonin* OR (calcitonin* ADJ3 (precursor* OR prohormone*)) OR (pct ADJ3 (value* OR level* OR marker* OR biomarker* OR blood* OR sample* OR collect*))).ab,ti.) AND (Emergencies/ OR exp Emergency Treatment/ OR emergency nursing/ OR exp Emergency Service, Hospital/ OR exp Emergency Medical Services/ OR exp emergency medicine/ OR traumatology/ OR multiple trauma/ OR (emergenc* OR acute care OR trauma* OR resuscitat* OR ed)) AND (english).la.

Cochrane central

((procalcitonin* OR (calcitonin* NEAR/3 (precursor* OR prohormone*)) OR (pct NEAR/3 (value* OR level* OR marker* OR biomarker* OR blood* OR sample* OR collect*))):ab,ti) AND ((emergenc* OR 'acute care' OR trauma* OR resuscitat* OR ed))

Web-of-science

TS=(((procalcitonin* OR (calcitonin* NEAR/3 (precursor* OR prohormone*)) OR (pct NEAR/3 (value* OR level* OR marker* OR biomarker* OR blood* OR sample* OR collect*)))) AND ((emergenc* OR "acute care" OR trauma* OR resuscitat* OR ed))) AND LA=(english)

PubMed as supplied by publisher

((Calcitonin[mh] AND Protein Precursors[mh]) OR (procalcitonin*[tiab] OR (calcitonin*[tiab] AND (precursor*[tiab] OR prohormone*[tiab])) OR (pct AND (value*[tiab] OR level*[tiab] OR marker*[tiab] OR biomarker*[tiab] OR blood*[tiab] OR sample*[tiab] OR collect*[tiab])))) AND (Emergencies[mh] OR Emergency Treatment[mh] OR emergency nursing[mh] OR Emergency Service, Hospital[mh] OR Emergency Medical Services[mh] OR emergency medicine[mh] OR traumatology[mh] OR multiple trauma[mh] OR (emergenc*[tiab] OR acute care OR trauma*[tiab] OR resuscitat*[tiab] OR ed[tiab])) AND english[la] AND publisher[sb]

Google scholar

Procalcitonin|"pct value|level|sample" emergency|traumatology|trauma|"acute care"

Supplement 2. Data extraction
First author, Year, Country, Journal, Hospital type, Single center/multicenter/ international multicenter, Study design, age distribution, gender distribution, ethnicity, inclusion criteria, exclusion criteria, PCT cut-off value used, overruling of PCT-algorithm, antibiotics reduction, hospital admission, length of hospital stay, ICU admission, ICU length of stay, return visits to ED, mortality, physician non-adherence with PCT advice.

Supplement 3: QUADAS 2 quality assessment **Review question**

Author	Year	Acronym	Title	Journal	Patients, index test, reference standard and target condition	Describe methods of patient selection:	Consecutive or random sample of patients enrolled? (off white = yes, black = no, gray = unclear)
G. Baer, P. Baumann, M. Buettcher, U. Heininger, G. Berthet, J. Schafer, H. C. Bucher, D. Trachsel, J. Schneider, M. Gambon, D. Reppucci, J. M. Bonhoeffer, J. Stahelin-Massik, P. Schuetz, B. Mueller, G. Szinnai, U. B. Schaad and J. Bonhoeffer	2013	ProPAED	Procalcitonin Guidance to Reduce Antibiotic Treatment of Lower Respiratory Tract Infection in Children and Adolescents (ProPAED): A Randomized Controlled Trial	PLoS ONE	Pediatric patients with LRTIs, PCT-guided therapy vs physician assessment and clinical guidelines, antibiotic prescribing rate, duration of antibiotics.	All patients between 1 month and 18 years of age with LRTIs were inlcuded. LRTI was defined with clinical criteria. Missed inclusions were registered.	
M. Christ-Crain, D. Jaccard-Stolz, R. Bingisser, M. M. Gencay, P. R. Huber, M. Tamm and B. Müller	2004		Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial	Lancet	Adult patients with suspected respiratory infections, PCT-guided therapy vs physician assessment, antibiotic prescribing rate.	All adult patients, presenting with dyspnoea, cough or both were eligible. Subpopulations based on clinical signs and symptoms.	
M. Christ-Crain, D. Stolz and R. Bingisser	2006	ProCAP	Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial	Am J Respir Crit Care Med	Adult ED patients with CAP, PCT-guided therapy vs physician assessment, antibiotic initiation and duration.	Adult patients with CAP admitted in the ED. Criteria were new infiltrate on chest X-ray, and presence of one or several acute respiratory signs and symptoms	
Drozdov, D. Schwarz, S. Kutz, A. Grolimund, E. Rast, A. C. Steiner, D. Regez, K. Schild, U. Guglielmetti, M. Conca, A. Reutlinger, B. Ottiger, C. Buchkremer, F. Haubitz, S. Blum, C. Huber, A. Buergi, U. Schuetz, P. Bock, A. Fux, C. A. Mueller, B. Albrich, W. C.	2015		Procalcitonin and pyuria-based algorithm reduces antibiotic use in urinary tract infections: A randomized controlled trial	BMC Med	Immunocompetent adults with UTI, PCT-pyuria treatment vs standard care, overall antibiotics exposure.	ED patients with non-catheter UTI	
Lacroix, L. Manzano, S. Vandertuin, L. Hugon, F. Galetto-Lacour, A. Gervaix, A.	2014		Impact of the lab-score on antibiotic prescription rate in children with fever without source: A randomized controlled trial	PLoS ONE	ED patients between 7 days and 3 years of age with fever, Lab score vs standard care, antibiotic prescription rate.	Parents of young children visiting tertiary ED were asked to participate.	A total of 1190 patients were assessed for eligibility, however, in 883 patients, participation was not offered. Reasons were not described
W. Long, X. Deng, Y. Zhang, G. Lu, J. Xie and J. Tang	2011		Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia	Respirology	ED patients between 18 and 65 years of age, with CAP that were discharged from ED, PCT-guided therapy vs physician assesment, antibiotic use and duration.	ED patients with CAP with PSI of I-III were eligible	
S. Manzano, B. Bailey, J. B. Girodias, A. Galetto-Lacour, J. Cousineau and E. Delvin	2010		Impact of procalcitonin on the management of children aged 1 to 36 months presenting with fever without source: A randomized controlled trial	Am J Emerg Med	Patients between 1 and 36 mnths of age visiting the ED with fever without source, PCT-guided vs standard care, antibiotics initiation.	Parents of patients with FWS were asked for participation when inclusion criteria were met. Randomisation usiong envelopes.	
P. Schuetz, M. Christ-Crain, R. Thomann, C. Falconnier, M. Wolbers, I. Widmer, S. Neidert, T. Fricker, C. Blum, U. Schild, K. Regez, R. Schoenenberger, C. Henzen, T. Bregenzer, C. Hoess, M. Krause, H. C. Bucher, W. Zimmerli and B. Mueller	2009	ProHOSP	Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: The ProHOSP randomized controlled trial	J Am Med Assoc	Adult ED patients with suspected LRTI, PCT-guided therapy vs standard care, composite safety endpoint, antibiotic exposure and duration, length of hospital stay.	ED patients with 1 respiratory symptom and 1 symptom of infection or auscultatory symptom.	
D. Stolz, M. Christ-Grain, R. Bingisser, J. Leuppi, D. Miedinger, C. Muller, P. Huber, B. Muller and M. Tamm	2007		Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy	Chest	ECOOPD patients of 40 years and older, PCT-guided therapy vs standard care, total antibiotics use at ED visit and 6 months after	ED patients with COPD who had specific post-bronchodilatator spirometry criteria.	
J. Tang, W. Long, L. Yan, Y. Zhang, J. Xie, G. Lu and C. Yang	2013		Procalcitonin guided antibiotic therapy of acute exacerbations of asthma: A randomized controlled trial	BMC Infect Dis	Adult asthma patients with exacerbation, PCT-guided therapy vs standard care, antibiotics use.	ED patients with criteria for asthma exacerbations.	

DOMAIN 2: Index test(s)

A. Risk of bias		B. Concerns regarding applicability		
If a threshold (cut-off value) was used, was it pre-specified? (off white = yes, black = no, gray = unclear)	**Could the conduct or interpretation of the index test have introduced bias? (RISK: off white = low, black = high, gray = unclear)**	**Is there concern that the index test, its conduct, or interpretation differ from the review question? (RISK: off white = low, black = high, gray = unclear)**	Describe the reference standard and how it was conducted and interpreted:	Is the reference standard likely to correctly classify the target condition? (off white = yes, black = no, gray = unclear)
	It is unclear what the final diagnosis of the febrile episode is. The choice of antibiotics in both the intervention and control group is based on ED assessment, but is not checked with the microbial etiology. Therefore the true indication of antibiotics cannot be verified.	A comparison between PCT per-protocol and intention-to-treat analysis would provide insight in PCT protocol adherence. Only an intention-to-treat analysis is provided, so non-adherence cannot be evaluated.	Reference standard was physician assessment in the ED, based on clinical guidelines.	
			Reference standard was physician assessment in the ED, and microbial laboratory investigations for final diagnosis.	
			Reference standard was physician assessment in the ED, based on clinical guidelines.	
		The review question is PCT guided therapy in the initiation of antibiotics in the ED. Because all patients received antibiotics initially, this study does not answer the primary review question.	Reference standard was physician assessment in the ED, based on clinical guidelines.	
		The study reports low adherence to Lab score recommendations. No reasons for nonadherence were reported.	Reference standard was physician assessment in the ED, based on clinical guidelines.	
			Reference standard was physician assessment in the ED, based on clinical guidelines.	
	The index test had a three-point-scale, either low, moderate or high risk of bacaterial infection. No antibiotic advice was given. Advice on antibiotics may have altered the results of antibiotic prescription or hospital admittance.		Reference standard was physician assessment in the ED, based on clinical guidelines.	
			Reference standard was physician assessment in the ED, based on clinical guidelines.	
			Reference standard was physician assessment in the ED, based on clinical guidelines.	
			Reference standard was physician assessment in the ED, based on clinical guidelines.	

DOMAIN 1: Patient selection

A. Risk of bias				B. Concerns regarding applicability		
Was a case-control design avoided? (off white = yes, black = no, gray = unclear)	Did the study avoid inappropriate exclusions (off white = yes, black = no, gray = unclear)	**Could the selection of patients have introduced bias? (RISK: off white = low, black = high, gray = unclear)**	Describe included patients (prior testing, presentation, intended use of index test and setting):	**Concern that included patients do not match review question? (RISK: off white = low, black = high, gray = unclear)**	Describe the index test and how it was conducted and interpreted:	*Were the index test results interpreted without knowledge of the reference standard? (off white = yes, black = no, gray = unclear)*
			Included pediatric patients all had fever (38.0 and up), with one additional symptom (tachypnea, dyspnoea, wheezing, late inspiratory crackles, bronchial breathing, pleural rub), and were without severe immunesuppression (HIC with low cd4+, immunesuppressive treatment, neutropenia, CF, acute croup, hospital stay within 14 days, or other severe infection. the index test determined if they would receive antibiotics.		PCT testing was performed in the lab using a Kryptor device. A previously described algorithm was used for interpretation, with predefined protocol violations, i.e. severe co-morbidity, ICU need, hemodynamic or respiratory instability	*Not applicable, the reference standard is physician assessment*
		47 patients were excluded because of "other" reasons, not specified, of the total of 597 eligible patients.	Included patients had cough and/or dyspnoea, and were without specific exclusioncriteria, chf, "other pulmonary disease, malignancy, immunocompromised status, or other types of infection. The index test determines if they will receive antibiotics.		PCT testing was performed in the lab using a Kryptor device. A previously described algorithm was used for interpretation, protocol violations were allowed on physician discretion without predefined criteria.	*Not applicable, the reference standard is physician assessment*
		Randomisation by envelopes, a method prone for randomisation bias.	Patients with suspected CAP present in the ED, the index test determines if they will receive antibiotics.		PCT testing was performed in the lab using a Kryptor device. A previously described algorithm was used for interpretation, protocol violations were allowed on physician discretion without predefined criteria.	*Not applicable, the reference standard is physician assessment*
		Randomisation by envelopes, a method prone for randomisation bias.	Immunocompetent patients visiting the ED, were divided in admitted and outpatient groups, and in simple/complicated UTI groups, the PCT level was used for the duration of treatment.	Because all patients received antibiotics initially, this study does not answer the research question.	PCT testing was performed in the lab. A previously described algorithm was used for interpretation, protocol violations were allowed on physician discretion without predefined criteria.	*Not applicable, the reference standard is physician assessment*
		Temperatures taken at home were used as inclusion criteria, these may not be reliable because there is no standard measurement technique.	Patients between 7 days and 3 years of age, who had fever of 38.0, measured either at home or in the ED, with no identified source of infection after history and physical examination, were eligible, parents gave informed consent. The Lab score was used to reduce antibiotics prescription.		The index test comprised of a PCT level (measured using VIDAS Brahms assay), CRP level, and urinary dipstick. Specific results determine a 9-points score.	*Not applicable, the reference standard is physician assessment*
		115 were excluded, but the reason for exclusion is not specified.	CAP patients who were treated as outpatient were included after ED visit. The index test determined if they would receive antibiotics.		PCT testing was performed in the lab using a Kryptor device. A previously described algorithm was used for interpretation, protocol violations were allowed on physician discretion without predefined criteria.	*Not applicable, the reference standard is physician assessment*
		Randomisation by envelopes, a method prone for randomisation bias.	Patients visiting a tertiary pediatric ED, who presented with history of a rectal temperature and where the physician required additional laboratory investigation (defined as fever without source after history and physical examination).	Fever based on history may not as reliable as an objective measurement.	PCT testing was performed using semiquantative PCT-Q test.	*Not applicable, the reference standard is physician assessment*
			Patients with suspected LRTIs of unknown etiology, the index test is to discriminate bacterial from non-bacterial origin		PCT testing was performed in the lab using a Kryptor device. A previously described algorithm was used for interpretation, protocol violations were allowed based on predefined criteria.	*Not applicable, the reference standard is physician assessment*
	Patients in whom there was found an alternative explanation other than AECOPD were excluded, also patients with psychiatric comorbidities were excluded.	By excluding patients with another explanation, the effect of the intervention will be exagerated. Psychiatric comorbidity may be associated with increased nonadherence to therapy. By excluding these patients, the effect also may be exaggerated.	Patients, older than 39 years, with ECOPD with specific spirometric criteria, without any other explanation of complaints, without psychiatric comorbidity or immunosuppression, asthma, CF or infiltrates on chest X-rays on admission. The index test determined if patients would receive antibiotics.		PCT testing was performed in the lab using a Kryptor device. A previously described algorithm was used for interpretation, protocol violations were allowed on physician discretion without predefined criteria.	*Not applicable, the reference standard is physician assessment*
		Randomisation by envelopes, a method prone for randomisation bias.	Adult asthma patients, following international asthma guidelines, without bacterial infection in other parts of body, confirmed pneumonia on chest X ray, other chronic respiratory diseases, or suffering from severe organ disfunction. The index test determined if patients would receive antibiotics.		PCT testing was performed in the lab using a Kryptor device. A previously described algorithm was used for interpretation, protocol violations were allowed on physician discretion without predefined criteria.	*Not applicable, the reference standard is physician assessment*

Domain 3: Reference standard					DOMAIN 4: Flow and timing				
A. Risk of Bias		B. Concerns regarding applicability			A. Risk of Bias				
Were the reference standard results interpreted without knowledge of the results of the index test? (off white = yes, black = no, gray = unclear)	**Could the reference standard, its conduct, or its interpretation have introduced bias? (RISK: off white = low, black = high, gray = unclear)**	**Is there concern that the target condition as defined by the reference standard does not match the review question? (RISK: off white = low, black = high, gray = unclear)**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):	Describe the time interval and any interventions between index test(s) and reference standard:	Was there an appropriate interval between index test(s) and reference standard? (off white = yes, black = no, gray = unclear)	Did all patients receive a reference standard? (off white = yes, black = no, gray = unclear)	Did patients receive the same reference standard? (off white = yes, black = no, gray = unclear)	Were all patients included in the analysis? (off white = yes, black = no, gray = unclear)	**Could the patient flow have introduced bias? (RISK: off white = low, black = high, gray = unclear)**
In the control group, the index test results were unknown.	Reference standard was physician assessment in determining initiation of antibiotics. The number of protocol violations in the PCT-guided group (low PCT, still antibiotics, based on physician assessment) are not described.		14 eligible patients who were excluded, were unable to give consent because of language problems with parents, 13 because of "other" reasons that were not specified.	tests were conducted simultaneously in the emergency department					
In the control group, the index test results were unknown.			Patients with chf, other pulmonary disease, hyperventilation, cerebral, URTI, allergy, thromboembolic event, carcinoma, immunocompromised, no-respiratory infection, and " others" were not deemed eligible	tests were conducted simultaneously in the emergency department					
In the control group, the index test results were unknown.			Excluded patients: did not meet CAP criteria, immunocompromised, TB, CF, HAP, not confirmed infiltrate by radiologist, died before randomisation, no informed consent	tests were conducted simultaneously in the emergency department					
In the control group, the index test results were unknown.			All included patients were analysed in the intention-to-treat analysis. They were excluded in the per-protocol analysis, the reasons of exclusion were described.	tests were conducted simultaneously in the emergency department					
In the control group, the index test results were unknown.			This study has not included more than 75% of eligible patients, because of either lack of time for logistics, and physician unwillingness to proceed in diagnostic tests in well appearing patients.	tests were conducted simultaneously in the emergency department					More than 75% of missed inclusions, without reporting of individual reasons.
In the control group, the index test results were unknown.			ED CAP patients who were not eligible for outpatient treatment were excluded, this is not specified	tests were conducted simultaneously in the emergency department					
In the control group, the index test results were unknown.			Patients whose parents did not consent were excluded. Also, in case of insufficient blood sampling, patients were exlcuded.	tests were conducted simultaneously in the emergency department					
In the control group, the indext test results were unknown.			237 patients were not eligible after screening, 12 eligible patients were screened because of "other" reasons, not specified	tests were conducted simultaneously in the emergency department					
In the control group, the index test results were unknown.			62 patients were excluded for analysis, 7 psychiatric patients, 7 with other not specified comorbidities, 3 with chest pain	tests were conducted simultaneously in the emergency department					There is a selection bias due to exclusion criteria.
In the control group, the index test results were unknown.			22 patients were excluded on exclusion criteria, not specified, 2 died before inclusion, 4 did not give informed consent	tests were conducted simultaneously in the emergency department					