Association of kidney function with effectiveness of procalcitonin-guided antibiotic treatment: a patient-level meta-analysis from randomized controlled trials

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Abstract

Objectives: Patients with impaired kidney function have a significantly slower decrease of procalcitonin (PCT) levels during infection. Our aim was to study PCT-guided antibiotic stewardship and clinical outcomes in patients with impairments of kidney function as assessed by creatinine levels measured upon hospital admission.

Methods: We pooled and analyzed individual data from 15 randomized controlled trials who were randomly assigned to receive antibiotic therapy based on a PCT-algorithms or based on standard of care. We stratified patients on the

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initial glomerular filtration rate (GFR, ml/min/1.73 m^2) in three groups (GFR >90 [chronic kidney disease; CKD 1], GFR 15–89 [CKD 2–4] and GFR<15 [CKD 5]). The main efficacy and safety endpoints were duration of antibiotic treatment and 30-day mortality.

Results: Mean duration of antibiotic treatment was significantly shorter in PCT-guided (n=2,492) compared to control patients (n=2,510) (9.5–7.6 days; adjusted difference in days –2.01 [95% CI, –2.45 to –1.58]). CKD 5 patients had overall longer treatment durations, but a 2.5-day reduction in treatment duration was still found in patients receiving in PCT-guided care (11.3 vs. 8.6 days [95% CI –3.59 to –1.40]). There were 397 deaths in 2,492 PCT-group patients (15.9%) compared to 460 deaths in 2,510 control patients (18.3%) (adjusted odds ratio, 0.88 [95% CI 0.78 to 0.98]). Effects of PCT-guidance on antibiotic treatment duration and mortality were similar in subgroups stratified by infection type and clinical setting (p interaction >0.05).

Conclusions: This individual patient data meta-analysis confirms that the use of PCT in patients with impaired kidney function, as assessed by admission creatinine levels, is associated with shorter antibiotic courses and lower mortality rates.

Keywords: antibiotic stewardship; chronic kidney disease; procalcitonin.

Introduction

Antibiotic stewardship has become an international priority to reduce risk of multi-resistant organisms and potential drug-related side effects for patients [1]. Among different other clinical and laboratory markers, procalcitonin (PCT) has emerged as an adjunct to clinical judgement to assess the risk for bacterial infection and treatment response to antibiotic therapy [2–4]. PCT is released by different tissues in the body in response to systemic inflammation caused by bacterial infections through cytokine stimulation (e.g., interleukin [IL]-1β, IL-6 or tumor necrosis factor [TNF]-α) [5–7]. The short time until PCT increases after bacterial infection and the kinetic profile, which differs in patients with and without response to infection [8], make PCT an interesting marker to monitor patients with infections and help to early reduce antibiotic treatment in case of a favorable clinical response [9, 10]. Multiple randomized studies found that antibiotic stewardship based on clinical judgement and PCT levels results in reduced antibiotic exposure, lower risk for side-effects and improvements in clinical outcomes including overall

survival [11–13]. Two patient data meta-analyses published in 2018 with focus on patients with respiratory tract infections [11, 14] and patients with sepsis [15] also confirmed associations of PCT-guidance and lower antibiotic consumption as well as improved health benefits. Still it is important to understand that PCT should be used only as an adjunct to clinical decision making since several factors and conditions may cause false positive and false negative results [16].

Kidney function has been identified as an important parameter that influences PCT kinetics. While PCT levels in healthy individuals are below the limit of detection, in patients with chronic kidney disease (CKD), elevated PCT levels and slower PCT kinetics have been reported [17–19]. This may be due to different potential reasons including low grade inflammation in CKD patients with a constant stimulation of PCT [20, 21] and a slower clearance of PCT due to impaired renal function. The importance of renal function on PCT kinetics, however, has been controversial with some reports not finding a significant effect of renal clearance on PCT [17, 22, 23], while a recently published case-control study reported a reduced PCT-clearance in patients with impaired kidney function [20]. Importantly, there is a lack of data from clinical trials investigating whether the effectiveness and safety of antibiotic stewardship based on PCT levels is possibly reduced in CKD patients.

Herein, we conducted a secondary analysis using data from an individual-patient data meta-analysis to assess the safety and efficacy of using PCT to guide antibiotic treatment decisions according to kidney function based on admission creatinine levels in patients with respiratory infections or sepsis included in previous randomized trials.

Materials and methods

Patient population and trial selection

We conducted a secondary analysis using our updated individual patient database [11, 14, 15, 24–27]. The study selection and data collection was based on the original protocol published in the Cochrane Library [28] and the report was prepared following the Preferred Reporting Items for Systematic Review and Meta-Analysis individual participant data guidelines [29, 30]. Overall, we selected individual patient data from 15 randomized controlled trials including patients with a clinical diagnosis of infection treated in the ICU or in the medical ward and information about kidney function. Hence, in accordance with the initial protocol, we excluded trials lacking information regarding kidney function as well as pediatric trials and those not using PCT for guiding the initiation and duration of antibiotic therapy.

Trial search and data collection

For this review the trial search was updated in February 2018 in collaboration with the Cochrane collaboration and conducted in all databases from the date of their inception to February 2018. In addition to the Cochrane Central Register for Controlled Trials (January 2017, Issue 1) databases searched included Medline Ovid (1966 to February 2017) and Embase (1980 to February 2017). All references were screened for eligibility and there were no language or publication restrictions. Two authors (Y.W. and M.A.M.) independently assessed trial eligibility based on titles, abstracts, and full-text reports, with further information being obtained directly from investigators as needed. Study protocols, case report forms, and unedited databases containing individual patient data were requested from investigators of all eligible trials. Data from each trial were first checked against reported results and queries were resolved with the principal investigator, trial data manager, or statistician. Data were assessed in a consistent manner across all trials, with standard definitions and parameters, and thus mortality rates differed slightly from previous reports. In accordance with the Cochrane methodology, we used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [31] approach to assess risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other types of bias. Initially, the grading was done by two authors (Y.W. and M.A.M.) and if conflicting, the grading was discussed with another author (P.S.) and within the meta-analysis group.

Patients and endpoints

In the final analysis we enrolled all patients with a known kidney function and a suspected or proven infection who had been included in a previous trial and were randomized either to PCT-guided care or a control group. There were no exclusion criteria except for lack of information regarding kidney function. The main efficacy endpoint was duration of antibiotic treatment within 30 days. The main safety endpoint was all-cause mortality within 30 days of randomization. In case of a shorter follow-up period, the available information in the trials was used (e.g., mortality at the time of hospital discharge). Secondary outcomes comprised length of hospital stay, length of ICU stay, and the need for kidney replacement therapy. The definition of and indication for renal replacement therapy was based on the definition used in the different trials.

Patients were divided into three groups according to the glomerular filtration rate (GFR) (estimated using the MDRD [Modification of Diet in Renal Disease] study equation) and based on the CKD (Chronic Kidney Disease) classification from the KDIGO (Kidney Disease Improving Global Outcomes) [32]. Patients with a GFR above or equal to 90 ml/min/1.73 m^2 were assigned to the group with normal kidney function, patients with a GFR between 15 and 89 ml/min/1.73 m^2 were assigned to the group with impaired renal function and patients with a GFR lower than 15 ml/min/1.73 m^2 were assigned to the group with end stage renal disease.

Statistical analysis

The statistical approach was similar to the previously published Cochrane Library study protocol [28] with additional stratification according to kidney function. Using multivariate hierarchical logistic regression [33, 34] we calculated odds ratios (ORs) and 95% confidence intervals (CIs) for the primary endpoint mortality. Variables in the multivariate analysis included treatment arm, age, treatment setting (ICU, medical ward) and type of infection. To control for within- and between-trial variability, a "trial" variable was added to the model as a random effect. For continuous and binary secondary endpoints, corresponding linear and logistic regression models were fitted, respectively. Patients were analyzed in groups to which they initially were randomly assigned and thus following the intention to treat principle. Predefined subgroup analyses were performed for type of infection, blood culture results, setting (ICU, medical ward) and the level of organ dysfunction (Sequential Organ Failure Assessment (SOFA)). All statistical analyses were done using STATA version 15.1 (StataCorp. College Station, Texas).

Results

Findings of systematic research and characteristics of included trials

A total of 990 records were identified in the initial search, of which 71 were assessed for eligibility and a total of 32 trials were potentially eligible for analysis. Seventeen trials were excluded due to lack of clinical data or information regarding kidney function. Within the remaining 15 trials, we excluded 1,833 from 6,835 individual patients due to missing information regarding creatinine values (Figure 1). Our final analysis thus consists of 5,002 individual patient records included in fifteen randomized controlled trials. The trials were conducted in nine different countries, namely Australia, Belgium, Brazil, Denmark, France, Germany, Italy, The Netherlands and Switzerland (Table 1). Eleven of these trials were multicentric, nine were performed in the ICU and six in the emergency department (ED) and medical ward. The three largest trials were the SAPS trial (n=1,516) [12], the ProHOSP trial (n=1,359) [35] and the SISPICT trial (n=1,089) [36]. The PCT algorithms used in the different trials were similar in concept and focused mainly on optimizing antibiotic tailoring by early stopping of therapy based on low PCT cutoff levels or a decrease in PCT from the peak by ≥80%. Adherence rates to PCT protocols were variable and ranged from 44 to 97%.

Baseline characteristics

Overall, 1,420 patients (28.4%) had a normal kidney function (CKD 1), 2,512 patients (50.2%) had an impaired renal function (CKD 2–4) and 1,070 patients (21.4%) had end stage renal disease (CKD 5).
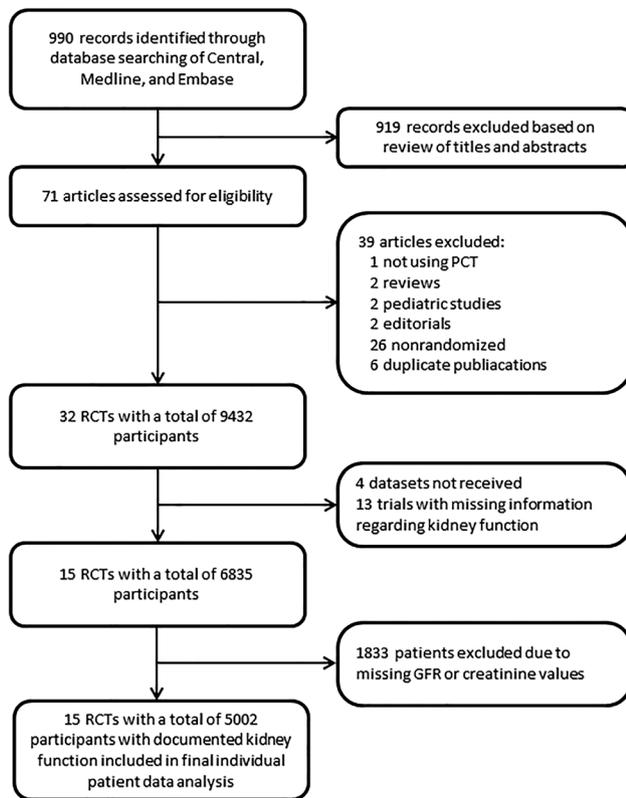
Figure 1: Study flowchart.
PCT, procalcitonin; RCT, randomized controlled trial; GFR, glomerular filtration rate.

Baseline characteristics of patients were overall similar in the PCT and control groups as well as in the different CKD subgroups. Table 2 and Supplementary Material, Appendix Table 1 shows baseline characteristics stratified according to randomization and kidney function. The most common infection focus was the respiratory tract in 29%. The SOFA scores and PCT values on admission were markedly higher in patients with worse kidney function. The majority of patients was treated in the ICU.

Primary efficacy endpoint: duration of antibiotic treatment

Mean duration of antibiotic treatment was significantly shorter in PCT-guided patients (n=2,492) compared to control patients (n=2,510) (7.6 vs. 9.5 days, adjusted difference −2.01 days [95% CI −2.45 to 1.58]). CKD 5 patients had overall longer treatment durations, but a 2.5-day treatment duration reduction was still found in PCT-guided patients (8.6 vs. 11.3 days [95% CI −3.59 to −1.40]). Effects were similar in subgroups stratified based on type of infection, blood culture result, treatment location (ICU vs. ward) and SOFA score (Figures 2, 3, Supplementary Material, Appendix Tables 2–4 and Appendix Figures 1 and 2).

Table 1: Characteristics of included trials.

First author (year)	Country	Type of trial	Setting	Patients included in original trial, n	Patients excluded, missing information regarding kidney function, n	Clinical diagnosis	Type of PCT algorithm and PCT cutoffs used, µg/L	Adherence to PCT protocol, %
Annane (2013)	France	Multicenter	ICU	62	52	Severe sepsis without overt source of infection and negative blood culture	Initiation and duration; R against AB: <0.5 (<0.25); R for AB: >0.5 (>0.5)	63%
Bouadma (ProRATA, 2010)	France	Multicenter	ICU	621	593	Critically ill patients with assumed/proven bacterial infection	Initiation and duration; R against AB: <0.5 (<0.25); R for AB: >0.5 (>0.1)	46%
Layios (2012)	Belgium	Single center	ICU	379	3	Critically ill patients with suspected infection	Initiation; R against AB: <0.5 (<0.25); R for AB: >0.5 (>1.0)	46.3%
Krisstoffersen (2009)	Denmark	Multicenter	ED, medical ward	210	208	Lower ARI without radiographic confirmation	Initiation and duration; R against AB: <0.25; R for AB: >0.25 (>0.5)	59%

Table 1: (continued)

First author (year)	Country	Type of trial	Setting	Patients included in original trial, n	Patients excluded, missing information regarding kidney function, n	Clinical diagnosis	Type of PCT algorithm and PCT cutoffs used, µg/L	Adherence to PCT protocol, %
Oliveira (2013)	Brazil	Multicenter	ICU	94	75	Severe sepsis or septic shock (SOFA score>10 and/or bacteremia)	Discontinuation; initial<1.0: R against AB: 0.1 at day 4; initial>1.0: R against: >90% drop over peak value	87.8%
Christ-Crain (ProCAP, 2006)	Switzerland	Single center	ED, medical ward	302	5	CAP with radiographic confirmation	Initiation and duration; R against AB: <0.25 (<0.1); R for AB: >0.25 (>0.5)	87%
Stolz (Pro-COLD, 2007)	Switzerland	Single center	ED, medical ward	208	174	COPD exacerbation according to the global initiative for chronic obstructive lung disease guidelines	Initiation and duration; R against AB: <0.25 (0.1); R for AB: > 0.25	Not reported
Christ-Crain (ProRESP, 2004)	Switzerland	Single center	ED	243	24	Lower ARI with radiographic confirmation	Initiation; R against AB: <0.25 (<0.1); R for AB: >0.25 (>0.5)	83%
De Jong (SAPS, 2016)	The Netherlands	Multicenter	ICU	1516	0	Critically ill patients with presumed infection	Duration; R against AB: <0.5 or >80% drop over peak value	44%
Bloss (SISPICT 2016)	Germany	Multicenter	ICU	1089	13	Severe sepsis and septic shock	Discontinuation at day 4, 7 and 10; R against AB: <1.0 or >50% drop to previous value	49.6%
Shehabi (2014)	Australia	Multicenter	ICU	394	355	Suspected sepsis, undifferentiated infections	Duration; R against AB: < 0.25 (<0.1) or > 90% drop	97%
Verduri (2015)	Italy	Multicenter	ED, medical ward	178	166	Acute COPD exacerbation	Initiation; R against AB: <0.1; R for AB: >0.25	Not reported
Nobre (2008)	Switzerland	Multicenter	ICU	79	71	Suspected severe sepsis or septic shock	Duration; R against AB: <0.5 (<0.25) or >80% drop; R for AB: >0.5 (>1.0)	81%
Schuetz (Pro-HOSP, 2009)	Switzerland	Multicenter	ED, medical ward	1359	50	Lower ARI with radiographic confirmation	Initiation and duration; R against AB: <0.25(<0.1); R for AB: >0.25 (>0.5)	91%
Stolz (ProVAP, 2009)	Switzerland	Multicenter	ICU	101	44	VAP when intubated>48 h	Duration; R against AB: <0.5 (0.25) or >80% drop; R for AB: >0.5 (>1.0)	Not reported

ICU, intensive care unit; ED, emergency department; AB, antibiotic; ARI, acute respiratory infection; SOFA, Sequential Organ Failure Assessment, COPD, Chronic obstructive pulmonary disease; VAP, ventilator-associated pneumonia; PCT, Procalcitonin; R, recommendation.

Table 2: Baseline characteristics of included patients.

Parameter	Patients with normal kidney function CKD stage G1		Patients with impaired kidney function			
			CKD stages G2–G4		CKD stage G5	
	Control (n=698)	PCT-group (n=722)	Control (n=1260)	PCT-group (n=1252)	Control (n=552)	PCT-group (n=518)
Age, years (mean ± SD)	56.2 (16.3)	55.3 (17.1)	68.8 (14.4)	68.8 (13.8)	71.8 (13.4)	72.8 (12.7)
Male sex	422 (60.5%)	431 (59.7%)	745 (59.1%)	768 (61.3%)	318 (57.6%)	309 (59.7)
Infect focus, n (%)						
Respiratory	273 (39.1%)	295 (40.9%)	373 (29.6%)	355 (28.4%)	88 (15.9%)	78 (15.1%)
Pneumoniae	139 (19.9%)	137 (19.0%)	332 (26.3%)	324 (25.9%)	184 (33.3%)	186 (35.9%)
COPD/bronchitis	64 (9.2%)	61 (8.4%)	134 (10.6%)	116 (9.3%)	78 (14.1%)	74 (14.3%)
URTI	5 (0.7%)	5 (0.7%)	4 (0.3%)	3 (0.2%)	–	–
Asthma	1 (0.1%)	3 (0.4%)	1 (0.1%)	4 (0.3%)	–	–
Urinary	16 (2.3%)	13 (1.8%)	35 (2.8%)	31 (2.5%)	25 (4.5%)	22 (4.2%)
Abdominal	56 (8.0%)	54 (7.5%)	201 (16.0%)	199 (15.9%)	77 (13.9%)	60 (11.6%)
Skin/soft tissue	10 (1.4%)	7 (1.0%)	15 (1.2%)	7 (0.6%)	8 (1.4%)	3 (0.6%)
Central nervous system	18 (2.6%)	14 (1.9%)	10 (0.8%)	16 (1.3%)	1 (0.2%)	2 (0.4%)
Genital/gynecologic	2 (0.3%)	0 (0.0%)	4 (0.3%)	3 (0.2%)	2 (0.4%)	0 (0.0%)
Catheter-related	5 (0.7%)	2 (0.3%)	5 (0.4%)	5 (0.4%)	0 (0.0%)	2 (0.4%)
Bloodstream	10 (1.4%)	6 (0.8%)	4 (0.3%)	4 (0.3%)	2 (0.4%)	4 (0.8%)
Others/Undifferentiated focus[a]	99 (14.2%)	125 (17.3%)	142 (11.3%)	185 (14.8%)	87 (15.8%)	87 (16.8%)
Setting, n (%)						
ED/medical ward	215 (30.8%)	213 (29.5%)	485 (38.5%)	467 (37.3%)	269 (48.7%)	265 (51.2%)
ICU	483 (69.2%)	509 (70.5%)	775 (61.5%)	785 (62.7%)	283 (51.3%)	253 (48.8%)
Vital signs						
Temperature, °C (mean ± SD)	37.9 (1.1)	38.0 (1.1)	37.8 (1.2)	37.9 (1.1)	37.8 (1.1)	37.9 (1.1)
Sepsis score						
SOFA score (points)	5.3 (3.6)	5.1 (3.3)	8.0 (3.7)	8.0 (3.9)	10.0 (3.8)	9.7 (4.0)
Laboratory assessments						
PCT day 0, μg/L (mean ± SD)	10.3 (41.7)	6.1 (25.4)	8.9 (23.2)	15.7 (45.0)	13.4 (31.6)	15.9 (41.7)
<0.1	113 (26.0%)	138 (19.5%)	116 (16.6%)	127 (10.8%)	35 (7.5%)	35 (7.2%)
0.1–0.25	78 (17.9%)	157 (22.1%)	147 (21.0%)	192 (16.3%)	72 (15.4%)	73 (15.1%)
0.25–0.5	41 (9.4%)	83 (11.7%)	72 (10.3%)	117 (9.9%)	51 (10.9%)	57 (11.8%)
0.5–2	75 (17.2%)	141 (19.9%)	106 (15.2%)	213 (18.1%)	84 (17.9%)	94 (19.4%)
>2	128 (29.4%)	190 (26.8%)	258 (36.9%)	530 (45.0%)	226 (48.3%)	226 (46.6%)
CRP day 0, mg/L (mean ± SD)	167.2 (123.0)	160.2 (120.1)	180.2 (126.5)	184.3 (130.7)	184.2 (131.6)	173.4 (133.6)
Creatinine, umol/L (mean ± SD)	47.7 (24.1)	45.3 (24.9)	121.0 (56.3)	121.5 (54.4)	232.5 (165.0)	238.7 (173.4)
Additional support, n (%)						
Vasopressor use	352 (72.7%)	375 (73.4%)	734 (94.7%)	732 (93.2%)	237 (85.6%)	208 (86.0%)
Ventilator support	386 (79.9%)	407 (79.6%)	634 (82.7%)	669 (85.5%)	210 (76.1%)	187 (76.3%)
Renal replacement	50 (7.2%)	60 (8.3%)	133 (10.6%)	124 (9.9%)	118 (21.4%)	101 (19.5%)

[a]Miscellaneous infections like endocarditis, mediastinitis, surgical wound infections or infection without a documented source.
ED, emergency department; ICU, intensive care unit; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; PCT, procalcitonin; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; URTI, upper respiratory tract infection; GFR, glomerular filtration rate; CKD, chronic kidney disease; ESRD, end stage renal disease.

Primary safety endpoint: mortality

Within 30 days there were 397 deaths in 2,492 PCT-guided patients (15.9%) compared to 460 deaths in 2,510 control-group patients (18.3%), resulting in an adjusted odds ratio for overall mortality of 0.88 (95% CI, 0.78–0.98; p=0.023). There was no evidence for effect modification according to CKD group, but patients with CKD stages 2–4 had the highest mortality benefit from PCT-guidance (14.6 vs. 20%, adjusted OR 0.74 [95% CI 0.63–0.87, p<0.001). Mortality effects were similar in subgroups stratified based on type of infection, blood culture result, treatment location (ICU vs. ward) and SOFA score (Figures 4, 5, Supplementary Material, Appendix Table 2).
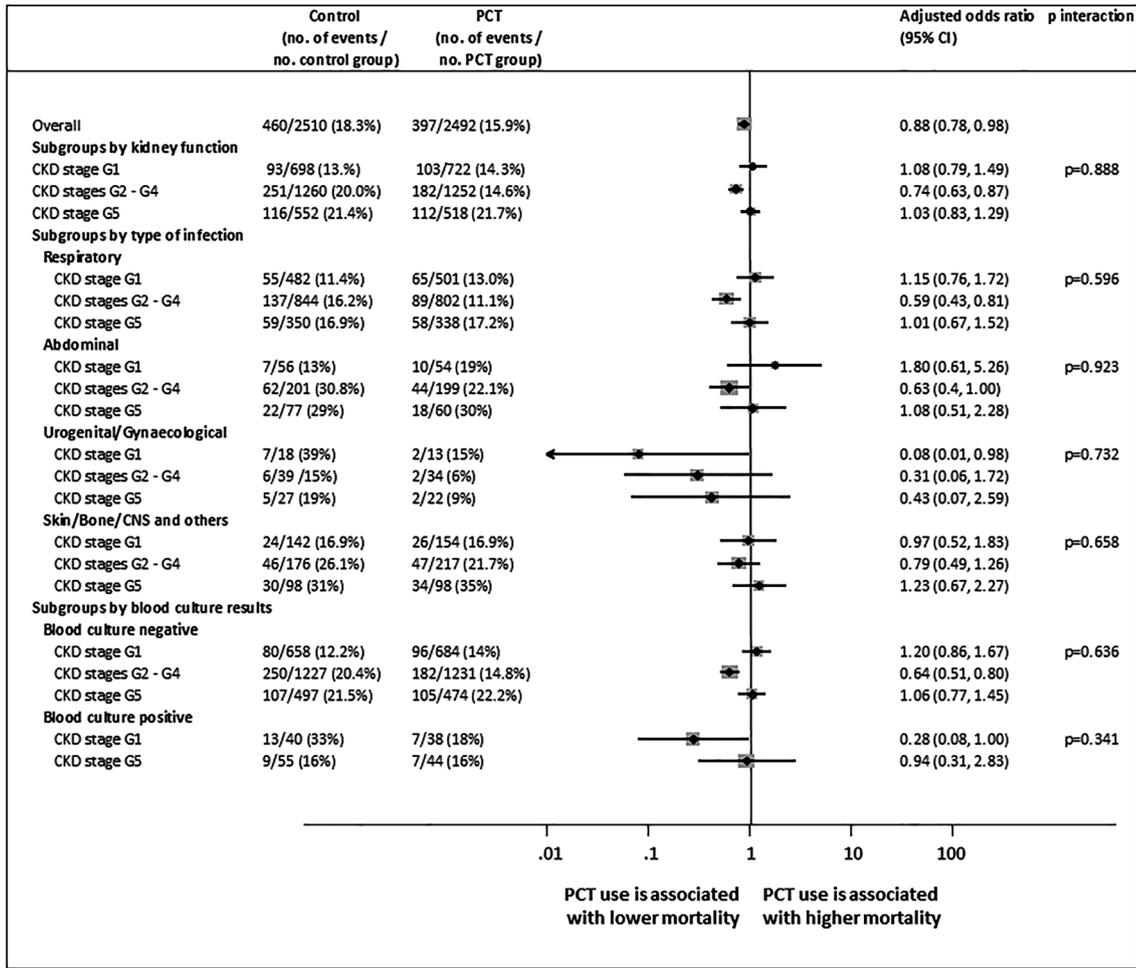
	Control (no. of events / no. control group)	PCT (no. of events / no. PCT group)		Adjusted odds ratio (95% CI)	p interaction
Overall	460/2510 (18.3%)	397/2492 (15.9%)		0.88 (0.78, 0.98)	
Subgroups by kidney function					
CKD stage G1	93/698 (13.%)	103/722 (14.3%)		1.08 (0.79, 1.49)	p=0.888
CKD stages G2 - G4	251/1260 (20.0%)	182/1252 (14.6%)		0.74 (0.63, 0.87)	
CKD stage G5	116/552 (21.4%)	112/518 (21.7%)		1.03 (0.83, 1.29)	
Subgroups by type of infection					
Respiratory					
CKD stage G1	55/482 (11.4%)	65/501 (13.0%)		1.15 (0.76, 1.72)	p=0.596
CKD stages G2 - G4	137/844 (16.2%)	89/802 (11.1%)		0.59 (0.43, 0.81)	
CKD stage G5	59/350 (16.9%)	58/338 (17.2%)		1.01 (0.67, 1.52)	
Abdominal					
CKD stage G1	7/56 (13%)	10/54 (19%)		1.80 (0.61, 5.26)	p=0.923
CKD stages G2 - G4	62/201 (30.8%)	44/199 (22.1%)		0.63 (0.4, 1.00)	
CKD stage G5	22/77 (29%)	18/60 (30%)		1.08 (0.51, 2.28)	
Urogenital/Gynaecological					
CKD stage G1	7/18 (39%)	2/13 (15%)		0.08 (0.01, 0.98)	p=0.732
CKD stages G2 - G4	6/39 /15%)	2/34 (6%)		0.31 (0.06, 1.72)	
CKD stage G5	5/27 (19%)	2/22 (9%)		0.43 (0.07, 2.59)	
Skin/Bone/CNS and others					
CKD stage G1	24/142 (16.9%)	26/154 (16.9%)		0.97 (0.52, 1.83)	p=0.658
CKD stages G2 - G4	46/176 (26.1%)	47/217 (21.7%)		0.79 (0.49, 1.26)	
CKD stage G5	30/98 (31%)	34/98 (35%)		1.23 (0.67, 2.27)	
Subgroups by blood culture results					
Blood culture negative					
CKD stage G1	80/658 (12.2%)	96/684 (14%)		1.20 (0.86, 1.67)	p=0.636
CKD stages G2 - G4	250/1227 (20.4%)	182/1231 (14.8%)		0.64 (0.51, 0.80)	
CKD stage G5	107/497 (21.5%)	105/474 (22.2%)		1.06 (0.77, 1.45)	
Blood culture positive					
CKD stage G1	13/40 (33%)	7/38 (18%)		0.28 (0.08, 1.00)	p=0.341
CKD stage G5	9/55 (16%)	7/44 (16%)		0.94 (0.31, 2.83)	

.01   .1   1   10   100

PCT use is associated   PCT use is associated
with lower mortality   with higher mortality

Figure 2: Forest plot showing 30-day mortality. Association of procalcitonin (PCT)-guided antibiotic stewardship and mortality in predefined subgroups.

No., number; CI, confidence interval; CDK, chronic kidney disease; CNS, central nervous system.

Secondary safety and efficacy endpoints

Need for renal replacement therapy

Overall, 285 of 2,492 (11.4%) patients in the PCT-guided group and 301 of 2,510 (12.0%) patients in the control group had acute renal failure and needed to undergo dialysis in the course of infection (adjusted OR 0.93 [95% CI 0.81–1.07], p=0.329). The risk for replacement therapy increased with CKD stage (7.8% in CKD 1, 10.2% in CKD 2–4, and 20.5% in CKD 5). Consistent with the overall finding, there were also no significant differences in renal replacement therapy rates between PCT-guided and control subjects throughout all subgroup analyses and no evidence of subgroup effect could be observed (p for interaction≥0.05, each)

(Supplementary Material, Appendix Tables 3 and 4, Appendix Figures 1 and 2).

Length of stay

Length of hospital stay as well as length of ICU stay did not significantly differ in the PCT-guided and the control group (overall 22.7 ± 25.3 vs. 23.4 ± 24.1 days, adjusted difference 0.64 [95% CI -0.65 to 1.93], p=0.329 and 15.1 ± 16.5 vs. 15.4 ± 17.0 days, adjusted regression coefficient 0.15 [95% CI –1.03 to 1.33], p=0.801, respectively) (Supplementary Material, Appendix Tables 5 and 6, Appendix Figures 3–6). This finding was similar across all subgroups without evidence for a subgroup effect (p for interaction≥0.05, each).
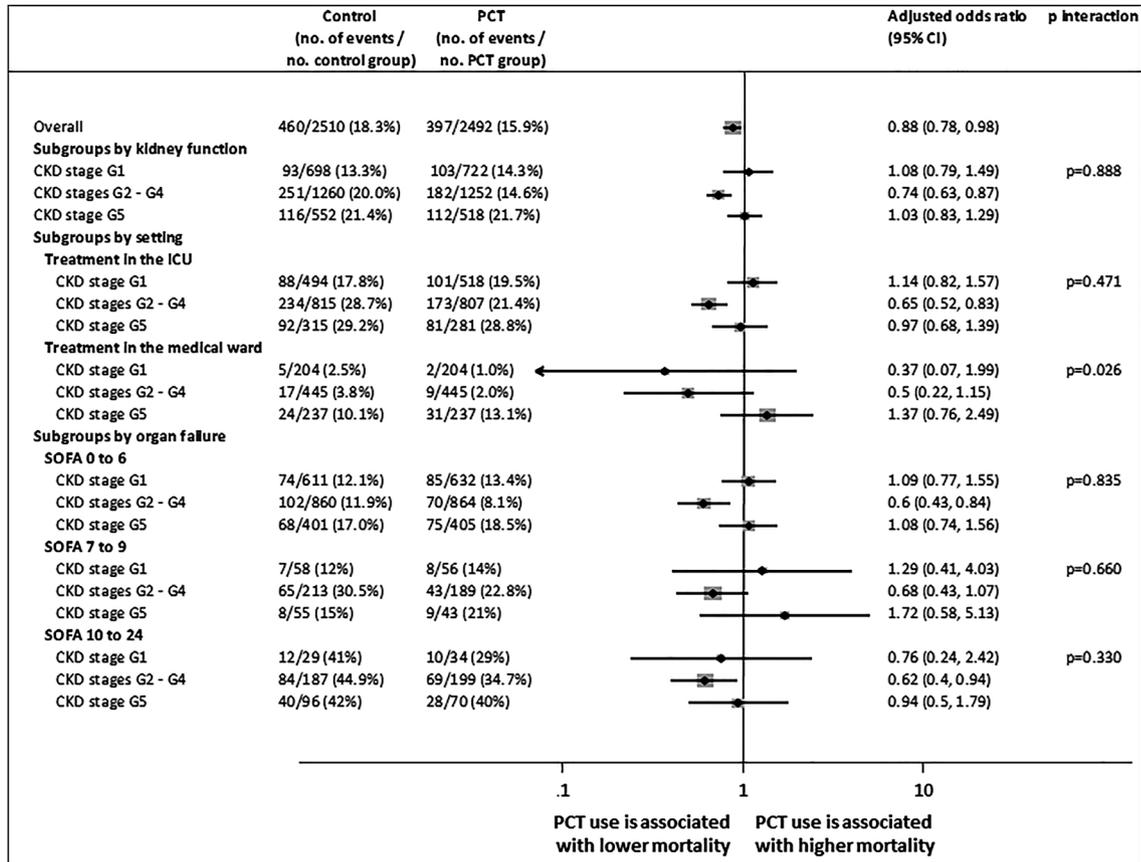
	Control (no. of events / no. control group)	PCT (no. of events / no. PCT group)		Adjusted odds ratio (95% CI)	p interaction
Overall	460/2510 (18.3%)	397/2492 (15.9%)		0.88 (0.78, 0.98)	
Subgroups by kidney function					
CKD stage G1	93/698 (13.3%)	103/722 (14.3%)		1.08 (0.79, 1.49)	p=0.888
CKD stages G2 – G4	251/1260 (20.0%)	182/1252 (14.6%)		0.74 (0.63, 0.87)	
CKD stage G5	116/552 (21.4%)	112/518 (21.7%)		1.03 (0.83, 1.29)	
Subgroups by setting					
Treatment in the ICU					
CKD stage G1	88/494 (17.8%)	101/518 (19.5%)		1.14 (0.82, 1.57)	p=0.471
CKD stages G2 – G4	234/815 (28.7%)	173/807 (21.4%)		0.65 (0.52, 0.83)	
CKD stage G5	92/315 (29.2%)	81/281 (28.8%)		0.97 (0.68, 1.39)	
Treatment in the medical ward					
CKD stage G1	5/204 (2.5%)	2/204 (1.0%)		0.37 (0.07, 1.99)	p=0.026
CKD stages G2 – G4	17/445 (3.8%)	9/445 (2.0%)		0.5 (0.22, 1.15)	
CKD stage G5	24/237 (10.1%)	31/237 (13.1%)		1.37 (0.76, 2.49)	
Subgroups by organ failure					
SOFA 0 to 6					
CKD stage G1	74/611 (12.1%)	85/632 (13.4%)		1.09 (0.77, 1.55)	p=0.835
CKD stages G2 – G4	102/860 (11.9%)	70/864 (8.1%)		0.6 (0.43, 0.84)	
CKD stage G5	68/401 (17.0%)	75/405 (18.5%)		1.08 (0.74, 1.56)	
SOFA 7 to 9					
CKD stage G1	7/58 (12%)	8/56 (14%)		1.29 (0.41, 4.03)	p=0.660
CKD stages G2 – G4	65/213 (30.5%)	43/189 (22.8%)		0.68 (0.43, 1.07)	
CKD stage G5	8/55 (15%)	9/43 (21%)		1.72 (0.58, 5.13)	
SOFA 10 to 24					
CKD stage G1	12/29 (41%)	10/34 (29%)		0.76 (0.24, 2.42)	p=0.330
CKD stages G2 – G4	84/187 (44.9%)	69/199 (34.7%)		0.62 (0.4, 0.94)	
CKD stage G5	40/96 (42%)	28/70 (40%)		0.94 (0.5, 1.79)	

.1   1   10

PCT use is associated   PCT use is associated
with lower mortality   with higher mortality

Figure 3: Forest plot showing 30-day mortality. Association of procalcitonin (PCT)-guided antibiotic stewardship and mortality in predefined subgroups.
No., number; CI, confidence interval; CDK, chronic kidney disease; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Discussion

The main findings of this meta-analysis including individual patient data from 5,002 participants from 15 randomized controlled trials are twofold. First, regarding efficacy, we found a significant reduction of antibiotic exposure due to shorter antibiotic treatment durations in PCT-guided patients in all kidney function subgroups. Although, CKD 5 patients had overall longer antibiotic courses, there was still a significant reduction observed in PCT-guided patients compared to the control group. Further, effects were similar in subgroups stratified by type of infection, blood culture results, site of treatment (medical ward vs. ICU), and disease severity according to SOFA score. Second, regarding safety, our overall analysis showed a significant reduction in mortality in PCT-guided patients compared to control group patients with different subgroup analyses showing similar results. Particularly, mortality and other safety outcomes were robust when stratified according to kidney function, by type of infection and by severity of illness.

Consistent with findings of previous studies, we found higher PCT levels in patients with impaired kidney function [17, 18, 20, 37]. There are different explanations for the higher PCT levels in patients with CKD. First, persistent low-grade inflammation could contribute to higher PCT baseline levels in CKD patients and impairment in kidney function itself trigger an inflammatory response that elevates PCT levels. Gupta et al. showed that plasma levels of several cytokines, especially IL-1β, IL-6 and TNF-α were increased in patients with impaired kidney function [38]. Hence, these cytokines may also induce expression of PCT by human epithelial cells throughout several tissues in the body. Second, a reduced renal clearance of both, stimulating inflammatory markers and PCT, may increase baseline as well as follow-up PCT levels too. Still, clinical data regarding the effects of renal function on PCT levels have been inconsistent. Meisner and colleagues examined the mechanisms of PCT elimination and revealed that even though the plasma clearance rate seems to be prolonged up to 30–50% in patients with kidney dysfunction, removal of PCT through the kidneys is not a major component [39]. In
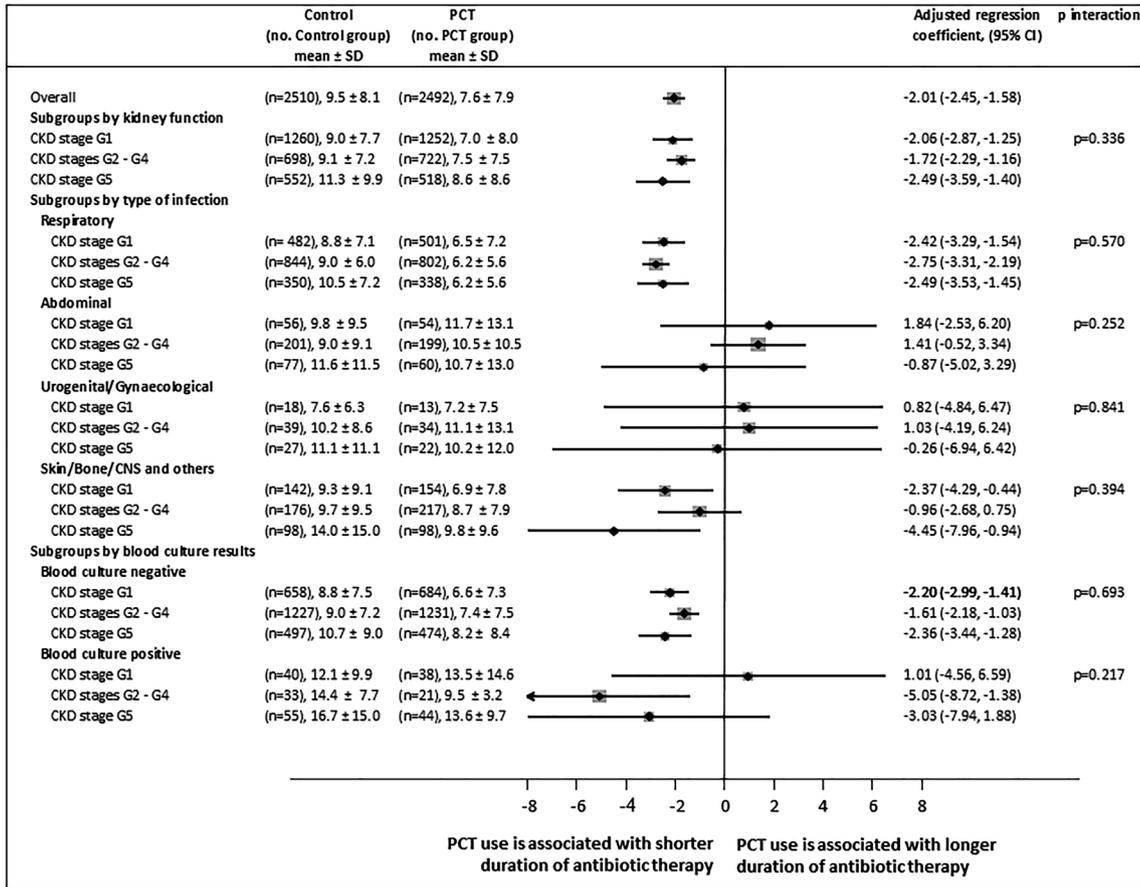
	Control (no. Control group) mean ± SD	PCT (no. PCT group) mean ± SD		Adjusted regression coefficient, (95% CI)	p interaction
Overall	(n=2510), 9.5 ±8.1	(n=2492), 7.6 ± 7.9		-2.01 (-2.45, -1.58)	
Subgroups by kidney function					
CKD stage G1	(n=1260), 9.0 ±7.7	(n=1252), 7.0 ± 8.0		-2.06 (-2.87, -1.25)	p=0.336
CKD stages G2 - G4	(n=698), 9.1 ± 7.2	(n=722), 7.5 ± 7.5		-1.72 (-2.29, -1.16)	
CKD stage G5	(n=552), 11.3 ± 9.9	(n=518), 8.6 ± 8.6		-2.49 (-3.59, -1.40)	
Subgroups by type of infection					
Respiratory					
CKD stage G1	(n= 482), 8.8 ± 7.1	(n=501), 6.5 ± 7.2		-2.42 (-3.29, -1.54)	p=0.570
CKD stages G2 - G4	(n=844), 9.0 ± 6.0	(n=802), 6.2 ± 5.6		-2.75 (-3.31, -2.19)	
CKD stage G5	(n=350), 10.5 ± 7.2	(n=338), 6.2 ± 5.6		-2.49 (-3.53, -1.45)	
Abdominal					
CKD stage G1	(n=56), 9.8 ± 9.5	(n=54), 11.7 ± 13.1		1.84 (-2.53, 6.20)	p=0.252
CKD stages G2 - G4	(n=201), 9.0 ± 9.1	(n=199), 10.5 ± 10.5		1.41 (-0.52, 3.34)	
CKD stage G5	(n=77), 11.6 ± 11.5	(n=60), 10.7 ± 13.0		-0.87 (-5.02, 3.29)	
Urogenital/Gynaecological					
CKD stage G1	(n=18), 7.6 ± 6.3	(n=13), 7.2 ± 7.5		0.82 (-4.84, 6.47)	p=0.841
CKD stages G2 - G4	(n=39), 10.2 ± 8.6	(n=34), 11.1 ± 13.1		1.03 (-4.19, 6.24)	
CKD stage G5	(n=27), 11.1 ± 11.1	(n=22), 10.2 ± 12.0		-0.26 (-6.94, 6.42)	
Skin/Bone/CNS and others					
CKD stage G1	(n=142), 9.3 ± 9.1	(n=154), 6.9 ± 7.8		-2.37 (-4.29, -0.44)	p=0.394
CKD stages G2 - G4	(n=176), 9.7 ± 9.5	(n=217), 8.7 ± 7.9		-0.96 (-2.68, 0.75)	
CKD stage G5	(n=98), 14.0 ± 15.0	(n=98), 9.8 ± 9.6		-4.45 (-7.96, -0.94)	
Subgroups by blood culture results					
Blood culture negative					
CKD stage G1	(n=658), 8.8 ± 7.5	(n=684), 6.6 ± 7.3		-2.20 (-2.99, -1.41)	p=0.693
CKD stages G2 - G4	(n=1227), 9.0 ± 7.2	(n=1231), 7.4 ± 7.5		-1.61 (-2.18, -1.03)	
CKD stage G5	(n=497), 10.7 ± 9.0	(n=474), 8.2 ± 8.4		-2.36 (-3.44, -1.28)	
Blood culture positive					
CKD stage G1	(n=40), 12.1 ± 9.9	(n=38), 13.5 ± 14.6		1.01 (-4.56, 6.59)	p=0.217
CKD stages G2 - G4	(n=33), 14.4 ± 7.7	(n=21), 9.5 ± 3.2		-5.05 (-8.72, -1.38)	
CKD stage G5	(n=55), 16.7 ± 15.0	(n=44), 13.6 ± 9.7		-3.03 (-7.94, 1.88)	

-8   -6   -4   -2   0   2   4   6   8

PCT use is associated with shorter duration of antibiotic therapy | PCT use is associated with longer duration of antibiotic therapy

Figure 4: Forest plot showing duration of antibiotic therapy. Association of procalcitonin (PCT)-guided antibiotic stewardship and duration of antibiotic therapy in predefined subgroups.
No., number; SD, standard deviation; CI, confidence interval; CDK, chronic kidney disease; CNS, central nervous system.

contrast, a recently published case-control study, conducted by Wu and colleagues, found an association between diminished kidney function and insufficient renal PCT-clearance [20]. They also observed a correlation between Cystatin C, a more precise marker of kidney function compared to creatinine, and PCT and argued for similar clearance mechanisms due to similar molecular properties of these two molecules. Our analysis does not provide any new insights regarding mechanisms of PCT-elimination. However, we also confirm higher PCT-levels and longer antibiotic treatment durations in patients with impaired kidney function independent of randomization arm, suggesting that kidney function influences levels of PCT at baseline and during follow-up. Third, patients with CKD may have a functionally declined immune system, resulting in more severe infections. As we know from multiple trials regarding septic patients, early and accurate diagnosis and differentiation from noninfectious causes are crucial for rapidly starting the appropriate initial treatment [40, 41]. This holds also true for patients with CKD and

associated comorbidities who are prone to severe infections, sepsis and septic shock. However, overuse of antibiotics in patients with viral instead of bacterial infection as well as unnecessarily long antibiotic duration are jointly responsible for the development of multidrug-resistant bacterial pathogens [42, 43]. Importantly, unnecessary administration and prolonged duration of antibiotic treatment contributes to antibiotic side effects and to a possible further impairment of kidney function and thus, worsening clinical outcomes. Hence, once antibiotic treatment is started, daily assessment of patients using clinical and objective parameters such as biomarkers is important. In recent years, PCT has been demonstrated to be a helpful adjunct to clinical judgement and traditional clinical parameters to decide whether to start antibiotic treatment and how long treatment should be continued. PCT levels increase within 6–12 h after bacterial invasion, are highest in patients with bacteremia, correlate with disease severity [24, 44] and rapidly fall by about 50% each day during resolution of infection. In contrast, PCT
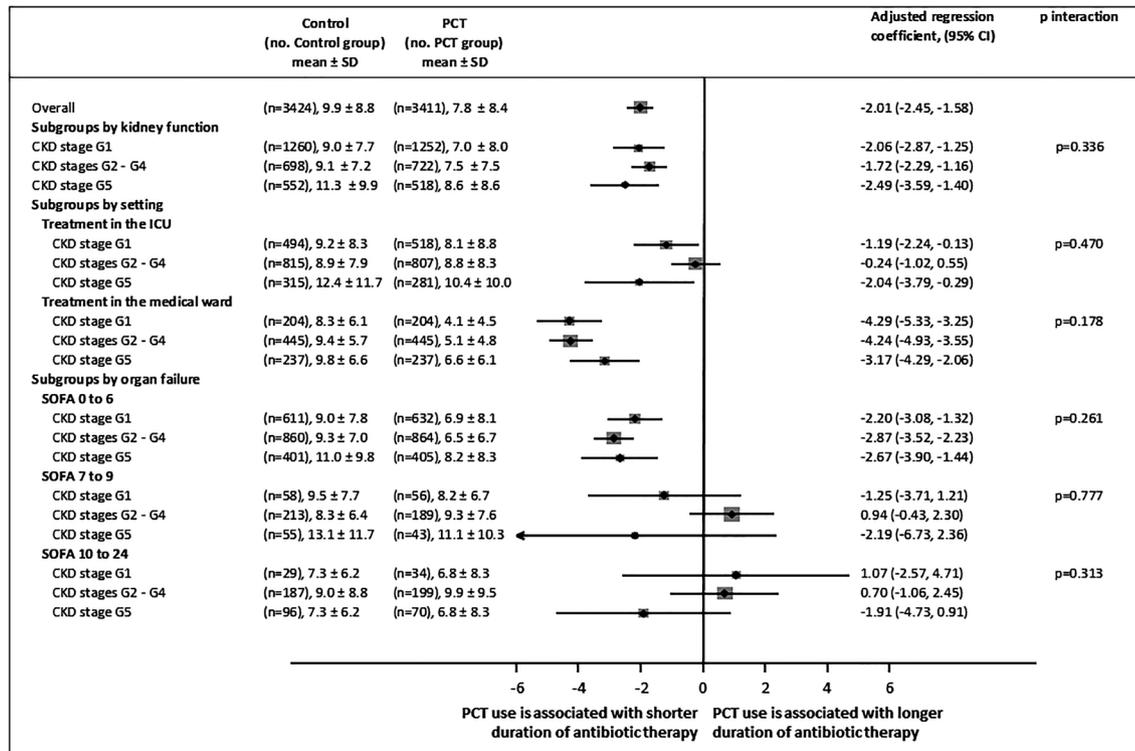
	Control (no. Control group) mean ± SD	PCT (no. PCT group) mean ± SD		Adjusted regression coefficient, (95% CI)	p interaction
Overall	(n=3424), 9.9 ± 8.8	(n=3411), 7.8 ± 8.4		-2.01 (-2.45, -1.58)	
Subgroups by kidney function					
CKD stage G1	(n=1260), 9.0 ± 7.7	(n=1252), 7.0 ± 8.0		-2.06 (-2.87, -1.25)	p=0.336
CKD stages G2 - G4	(n=698), 9.1 ± 7.2	(n=722), 7.5 ± 7.5		-1.72 (-2.29, -1.16)	
CKD stage G5	(n=552), 11.3 ± 9.9	(n=518), 8.6 ± 8.6		-2.49 (-3.59, -1.40)	
Subgroups by setting					
Treatment in the ICU					
CKD stage G1	(n=494), 9.2 ± 8.3	(n=518), 8.1 ± 8.8		-1.19 (-2.24, -0.13)	p=0.470
CKD stages G2 - G4	(n=815), 8.9 ± 7.9	(n=807), 8.8 ± 8.3		-0.24 (-1.02, 0.55)	
CKD stage G5	(n=315), 12.4 ± 11.7	(n=281), 10.4 ± 10.0		-2.04 (-3.79, -0.29)	
Treatment in the medical ward					
CKD stage G1	(n=204), 8.3 ± 6.1	(n=204), 4.1 ± 4.5		-4.29 (-5.33, -3.25)	p=0.178
CKD stages G2 - G4	(n=445), 9.4 ± 5.7	(n=445), 5.1 ± 4.8		-4.24 (-4.93, -3.55)	
CKD stage G5	(n=237), 9.8 ± 6.6	(n=237), 6.6 ± 6.1		-3.17 (-4.29, -2.06)	
Subgroups by organ failure					
SOFA 0 to 6					
CKD stage G1	(n=611), 9.0 ± 7.8	(n=632), 6.9 ± 8.1		-2.20 (-3.08, -1.32)	p=0.261
CKD stages G2 - G4	(n=860), 9.3 ± 7.0	(n=864), 6.5 ± 6.7		-2.87 (-3.52, -2.23)	
CKD stage G5	(n=401), 11.0 ± 9.8	(n=405), 8.2 ± 8.3		-2.67 (-3.90, -1.44)	
SOFA 7 to 9					
CKD stage G1	(n=58), 9.5 ± 7.7	(n=56), 8.2 ± 6.7		-1.25 (-3.71, 1.21)	p=0.777
CKD stages G2 - G4	(n=213), 8.3 ± 6.4	(n=189), 9.3 ± 7.6		0.94 (-0.43, 2.30)	
CKD stage G5	(n=55), 13.1 ± 11.7	(n=43), 11.1 ± 10.3		-2.19 (-6.73, 2.36)	
SOFA 10 to 24					
CKD stage G1	(n=29), 7.3 ± 6.2	(n=34), 6.8 ± 8.3		1.07 (-2.57, 4.71)	p=0.313
CKD stages G2 - G4	(n=187), 9.0 ± 8.8	(n=199), 9.9 ± 9.5		0.70 (-1.06, 2.45)	
CKD stage G5	(n=96), 7.3 ± 6.2	(n=70), 6.8 ± 8.3		-1.91 (-4.73, 0.91)	

PCT use is associated with shorter duration of antibiotic therapy — PCT use is associated with longer duration of antibiotic therapy

Figure 5: Forest plot showing duration of antibiotic therapy. Association of procalcitonin (PCT)-guided antibiotic stewardship and duration of antibiotic therapy in predefined subgroups.
No., number; SD, standard deviation; CI, confidence interval; CDK, chronic kidney disease; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

expression is blocked by cytokines, which are typically released in response to viral infection, making it a more specific parameter to differentiate between bacterial and viral infection [5, 45]. Several studies investigating the diagnostic accuracy of PCT yielded diverging results [46, 47]. However, observational studies found sensitivities and specificities of around 80%, which could be increased using algorithms containing a variety of PCT-cutoff points in combination with clinical criteria [3, 48]. Regarding safety of usage of such a PCT-algorithm, two different patient-level meta-analyses of high quality randomized controlled trials on patients with acute respiratory infections and critical illness showed improved survival, when antibiotic treatment was based on PCT-values [11, 15]. In the safety assessment, our study showed no difference in mortality between the PCT-guided and the control group. But the reduced antibiotic treatment durations as well as no obvious difference in need for renal replacement therapy, length of hospital and length of ICU stay, did not reveal any associated harm. Therefore, it is helpful to use PCT to guide antibiotic stewardship in patients with CKD, but due to the finding of significant increased levels of PCT

in patients with CKD even without infection, higher cutoff values seem reasonable. The earlier mentioned case-control study by Wu et colleagues revealed a 94.7% sensitivity and 90.8% specificity with the use of a PCT cutoff value of 0.075 ng/mL.

Our analysis supports the use of PCT in patients with impaired kidney function and is in line with several previous studies [11, 25, 26]. In PCT-guided patients, antibiotic therapy was shortened by an average of 2 days. This effect tended to be more pronounced in patients with end stage renal disease and those suffering from respiratory tract infections. These effects were not significant in all subgroups due to small sample sizes, but the negative interaction test points to robust results. Clearly, more data is needed to look at specific patient populations, which were underrepresented in our analysis despite the individual data meta-analysis approach.

The strength of this meta-analysis includes a predefined study protocol, a comprehensive search and retrieval of all relevant trials, and a network that permitted inclusion of individual patient data from most eligible trials. We also standardized outcome definitions across trials and performed appropriate subgroup and sensitivity

analyses, thereby overcoming the limitations of previous meta-analyses with aggregated data to allow more definitive conclusions. To our knowledge, this is the first analysis addressing the effects of PCT-guidance in patients with CKD.

However, there are some limitations of our study. First, we limited our data to immunocompetent adults and patients not being on hemodialysis before inclusion, thereby reducing generalisability of our conclusions to other patient populations. Second, the heterogeneity of our patient population with regard to focus of infection, clinical setting and disease severity, also limits generalisability of results, in particular with regard to the primary endpoint mortality. Third, the adherence to the PCT-protocols among the studies varied widely from 44 to 97%. Overall, adherence rates were better in low-risk populations, whereas the adherence in high-risk patients was lower. This can be explained by the fact, that in case of clinically seriously ill patients, physicians tend to decide rather on clinical findings than on laboratory results. Because of the fact, that low adherence may interfere with the effects of PCT-protocols, it is important that physicians are educated regarding correct and beneficial use of PCT [49]. Finally, we had very limited data on kidney function for individual patients due to the heterogeneity of trials and thus based our analysis on the initial creatinine level. Particularly, we were not able strictly separate acute from chronic conditions and also do not know how kidney function changed over the course of the hospital stay. This data would also provide important information to better understand the influence of kidney function and its recovery on levels of PCT and associated clinical effects regarding antibiotic use and outcome.

Conclusions

In conclusion, this individual patient data meta-analysis confirms that in patients with impaired kidney function, estimated based on admission creatinine levels, the use of PCT is associated with shorter antibiotic treatment durations without any apparent harm.

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