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SYSTEMATIC REVIEW

Duration of antibiotic treatment using procalcitonin-guided treatment algorithms in older patients: a patient-level meta-analysis from randomized controlled trials

Eva Heilmann[1,2], Claudia Gregoriano[1,2], Djillali Annane[3], Konrad Reinhart[4,5], Lila Bouadma[6], Michel Wolff[6], Jean Chastre[6], Charles-Edouard Luyt[7], Florence Tubach[8], Angela R. Branche[9], Matthias Briel[10], Mirjam Christ-Crain[11], Tobias Welte[12], Caspar Corti[13], Evelien de Jong[14], Maarten Nijsten[15], Dylan W. de Lange[16], Jos A.H. van Oers[17], Albertus Beishuizen[18], Armand R. J. Girbes[14], Rodrigo O. Deliberato[19], Stefan Schroeder[20], Kristina B. Kristoffersen[21], Nathalie Layios[22], Pierre Damas[22], Stella S. S. Lima[23], Vandack Nobre[23], Long Wei[24], Carolina F. Oliveira[23], Yahya Shehabi[25,26], Daiana Stolz[27], Michael Tamm[27], Alessia Verduri[28], Jin-Xiang Wang[29], Sabine Drevet[30], Gaetan Gavazzi[30], Beat Mueller[1,31], Philipp Schuetz[1,31]

[1]Medical University Department, Kantonsspital Aarau, Aarau, Switzerland
[2]Department of Oncology, Kantonsspital Aarau, Aarau, Switzerland
[3]Department of Critical Care, Hyperbaric Medicine and Home Respiratory Unit, Center for Neuromuscular Diseases, Raymond Poincaré Hospital (AP-HP), Garches, France
[4]Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany
[5]Clinical Trial Centre Leipzig, University of Leipzig, Leipzig, Germany
[6]Service de Réanimation Médicale, Assistance Publique-Hôpitaux de Paris (AP-HP), Univeersité Paris 7-Denis-Diderot, Paris, France
[7]Service de Médecine Intensive Réanimation, Assistance Publique-Hôpitaux de Paris (AP-HP), Sorbonne Université, Paris, France
[8]Département d'Epidémiologie Biostatistique et Recherche Clinique, AP-HP, Hôpitaux Universitaires Paris Nord Val de Seine, Paris, France
[9]Department of Medicine, Rochester General Hospital, New York, NY, USA
[10]Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland
[11]Division of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Basel, Basel, Switzerland
[12]Department of Pulmonary Medicine, Medizinische Hochschule Hannover, Hannover, Germany
[13]Department of Respiratory Medicine, Hospital Bispebjerg, Copenhagen University, Copenhagen, Denmark
[14]Department of Intensive Care, VU University Medical Center, Amsterdam, the Netherlands
[15]University Medical Centre, University of Groningen, Groningen, the Netherlands
[16]University Medical Center Utrecht, Utrecht, the Netherlands
[17]Department of Intensive Care Medicine, Elisabeth Tweesteden Hospital, Tilburg, the Netherlands
[18]Medisch Spectrum Twente, Enschede, the Netherlands
[19]Critical Care Unit, Hospital Israelita Albert Einstein, São Paulo, Brazil
[20]Department of Anesthesiology and Intensive Care Medicine, Krankenhaus Dueren, Dueren, Germany
[21]Department of Infectious Diseases, Aarhus University Hospital, Aarhus N, Denmark
[22]Department of General Intensive Care, University Hospital of Liege, Domaine Universitaire de Liège, Liege, Belgium
[23]Department of Internal Medicine, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil
[24]Department of Medicine, Shanghai Fifth People's Hospital, Shanghai, China
[25]Critical Care and Peri-operative Medicine, Monash Health, Melbourne, Australia
[26]Faculty of Medicine Nursing and Health Sciences, School of Clinical Sciences, Monash University, Melbourne, Australia
[27]Clinic of Pneumology and Pulmonary Cell Research, University Hospital Basel, Basel, Switzerland
[28]Department of Medical and Surgical Sciences, Policlinico di Modena, University of Modena and Reggio Emilia, Modena, Italy

[29]Department of Respiratory and Critical Care Medicine, Beijing Luhe Hospital, Capital Medical University, Beijing, China
[30]University Clinics of Geriatrics, University Hospital of Grenoble-Alpes, GREPI TIMC-IMAG CNRS 5525 University of Grenoble Alpes, Grenoble, France
[31]Faculty of Medicine, University of Basel, Basel, Switzerland

Address correspondence to: Philipp Schuetz, University Department of Medicine, Kantonsspital Aarau, Tellstrasse, CH-5001 Aarau, Switzerland. Tel: +41 (0) 62 838 41 41. Email: schuetzph@gmail.com

Abstract

Background: Older patients have a less pronounced immune response to infection, which may also influence infection biomarkers. There is currently insufficient data regarding clinical effects of procalcitonin (PCT) to guide antibiotic treatment in older patients.
Objective and design: We performed an individual patient data meta-analysis to investigate the association of age on effects of PCT-guided antibiotic stewardship regarding antibiotic use and outcome.
Subjects and methods: We had access to 9,421 individual infection patients from 28 randomized controlled trials comparing PCT-guided antibiotic therapy (intervention group) or standard care. We stratified patients according to age in four groups (<75 years [$n = 7{,}079$], 75–80 years [$n = 1{,}034$], 81–85 years [$n = 803$] and >85 years [$n = 505$]). The primary endpoint was the duration of antibiotic treatment and the secondary endpoints were 30-day mortality and length of stay.
Results: Compared to control patients, mean duration of antibiotic therapy in PCT-guided patients was significantly reduced by 24, 22, 26 and 24% in the four age groups corresponding to adjusted differences in antibiotic days of −1.99 (95% confidence interval [CI] −2.36 to −1.62), −1.98 (95% CI −2.94 to −1.02), −2.20 (95% CI −3.15 to −1.25) and − 2.10 (95% CI −3.29 to −0.91) with no differences among age groups. There was no increase in the risk for mortality in any of the age groups. Effects were similar in subgroups by infection type, blood culture result and clinical setting (P interaction >0.05).
Conclusions: This large individual patient data meta-analysis confirms that, similar to younger patients, PCT-guided antibiotic treatment in older patients is associated with significantly reduced antibiotic exposures and no increase in mortality.

Keywords: age, older patients, procalcitonin, antibiotic stewardship

Key Points

- PCT-guided antibiotic treatment significantly reduced antibiotic exposures in older patients without increasing mortality in older patients.
- PCT-guided antibiotic treatment did not lead to higher mortality in older patients.
- Despite differences in the immune response in older patients, a biomarker strategy to guide antibiotic treatment is feasible.

Introduction

Sepsis remains a major healthcare problem worldwide and is responsible for a large number of deaths particularly in the older patient population [1, 2]. Early identification and appropriate initial management, including start of antibiotic treatment and fluid resuscitation, have been shown to improve outcomes [2, 3]. In addition, monitoring of patients during treatment both for timely escalation of therapy in case of treatment failure and de-escalation in case of a favourable treatment response has an important impact on patients' recovery [2]. This also includes early de-escalation or cessation of antibiotic treatment once a patient's condition has stabilized, with signs indicating progression towards resolution of infection. In addition to closely monitoring the clinical status of patients, blood biomarkers mirroring specific physiopathological pathways may help to better estimate the resolution of infection thereby improving clinical decision-making [4–6]. Serum procalcitonin (PCT) has emerged as a host-derived biomarker that provides prognostic information in patients with infections and thus may improve sepsis management [7, 8]. Particularly, the kinetics of PCT in an infected patient provide information about the recovery and risk for adverse outcome, which in turn may influence decisions about the duration of antibiotic treatment [7–9]. Multiple randomized controlled trials (RCT) have investigated the benefits of using serum PCT levels to guide whether and for how long antibiotic therapy is used—a process referred to as PCT-guided antibiotic stewardship—in patients with different types of infections including sepsis patients in intensive care unit (ICU) [1, 10–20]. There are several trials and meta-analyses from such trials suggesting

that PCT use decreases antibiotic exposure with beneficial effects on clinical outcomes including lower mortality in patients with respiratory tract infections, sepsis and blood stream infection [21–25].

Still, it remains unclear whether data from these trials are also true for older patients who might have a different cytokine and biomarker response to infection compared to younger patients [26, 27]. Older patients may have often impairment in kidney function, which may affect biomarker kinetics, but has not been shown to impact on PCT-guided stewardship efforts in a previous analysis [28]. Also, older patients have a less pronounced immune response to infection and important differences in regard to the adaptive and innate immunity have been well documented [26]. As a result, older patients may not present with fever and clinical signs of inflammation/infection compared to younger patients, but their mortality risk associated with infection and sepsis is much higher compared to younger patients [29, 30]. This also may impact the clinical interpretation of different biomarkers of infection in this group of patients. There is an important lack of conclusive evidence on the efficacy and safety of PCT for antibiotic stewardship across different age groups [31]. Previous individual trials have had limited statistical power regarding different age subgroups. In addition, traditional aggregate data meta-analyses have been inconclusive as no age stratification was possible [32, 33].

To address this significant drawback of earlier meta-analyses and to understand whether patient age would have an influence on the efficacy and safety of PCT protocols to guide antibiotic treatment, we did a secondary analysis of a previously published meta-analysis of individual patient data from 28 RCTs in patients with different types and severities of infection stratified in four different age groups. The main finding of the meta-analysis regarding effects of PCT use in patients with respiratory infections has been published previously [22, 34], as well as other analyses looking specifically at specific subgroups of patients with sepsis [21] and patients with positive blood cultures [35], and associations of admission kidney function on PCT use [28]. We contacted the authors of 28 RCTs identified in the earlier meta-analysis [22, 34] in order to obtain their original datasets. We analysed these datasets in the current study to determine whether PCT-guided therapy was associated with a change in duration of antibiotic therapy specifically in the >75-year-old age group.

Methods

Role of funding source

The initial Cochrane analysis received funding from the National Institute for Health Research and several included trials received funding from industry regarding free-of-charge kits for measurement of PCT. For this study, an unrestricted grant was provided by Thermo-Fisher Scientific. This was an investigator-initiated study and Thermo-Fisher Scientific had no bearing on study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Patient population and trial selection

We used an existing individual patient database from 2017 [21–23, 34–37] and updated the underlying search in February 2018 but did not find new trials which could have been included. We performed a secondary meta-analysis focusing on PCT-guided antibiotic therapy in older patients. Study selection and data collection were done according to the original protocol published in the Cochrane Library [25], and the report was prepared following the Preferred Reporting Items for Systematic Review and Meta-Analysis individual participant data guidelines [38, 39]. Individual patient data were extracted from 28 RCTs including patients with proven or suspected infection treated in three different settings (ICU, medical ward and primary care) and whose age was documented. Consequently, according to the initial protocol, trials lacking information regarding patient age were excluded from analysis as well as paediatric trials and those not using a PCT algorithm to guide antibiotic therapy. There was no information regarding frailty available in trials.

Search strategy and selection criteria

In collaboration with the Cochrane collaboration, the trial search was updated in February 2018 and undertaken in all databases from the date of their inception to February 2018. Overall, databases searched included the Cochrane Central Register for Controlled Trials (January 2017, Issue 1), 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. Based on titles, abstracts and full-text reports, two authors Yannick Wirz (Bürgerspital Solothurn, Switzerland) and Marc A. Meier (Triemli Spital, Zuerich, Switzerland) independently assessed eligibility of the trials. As needed, further information was directly obtained from investigators. In case of eligibility, study protocols, case report forms and unedited databases containing individual patient data were requested from investigators. Data from each trial were checked against reported results and queries were resolved with the principal investigator, trial data manager or statistician. Across all trials, data were rated in a uniform manner with standard definitions and parameters. Thus, mortality rates differed slightly from previous reports. To assess the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias and other types of bias, we used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [40] in accordance with the Cochrane methodology and have published detailed information risk of bias previously [22]. The grading was done by two authors (Y.W. and M.A.M.) and if needed discussed with another author (P.S.) and within the meta-analysis group.

Patients and endpoints

In our final meta-analysis, we included patients suffering from proven or suspected infection whose age was known and who had been enrolled in a previous trial being randomized either to PCT-guided therapy or to a control group.

The primary endpoint was the duration of antibiotic treatment (in days). Secondary endpoints included 30-day mortality and length of hospital and ICU stay 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).

To assess the effect of PCT guidance in older people and in accordance with the diversity of older people, patients were divided into four different age subgroups. Patients younger than 75 years were classified as young-olds, patients >85 years were classified as old-olds and patients between 75 and 85 years of age were classified as middle-olds and further divided into a group of 75–80 years and 81–85 years.

Statistical analysis

All statistical analyses were done using STATA version 15.1 (StataCorp., College Station, TX). Following the statistical approach of the previously published Cochrane Library study protocol with additional stratification according to age, we used multivariable hierarchical logistic regression [41, 42] to analyse the association between primary and secondary outcomes and age, type of infection, treatment arm and treatment setting, which were reported as odds ratios (ORs) and 95% confidence intervals (CIs). A 'trial' variable was added to the model as a random effect in order to control for within- and between-trial variability. Corresponding linear and logistic regression models were adapted for continuous and binary secondary endpoints, respectively. According to the intention-to-treat principle, patients were analysed in the groups to which they initially were randomly assigned. Additional predefined subgroup analyses were performed for type of infection, blood culture results, treatment setting (ICU, medical ward, primary care) and the level of organ dysfunction (Sequential Organ Failure Assessment [SOFA]).

Results

Systemic research and characteristics of included trials

Study flowchart is presented in Figure 1. The initial study search identified a total of 990 records, 71 of which were assessed for eligibility and 32 of which in turn were potentially eligible for the analysis. Overall, we excluded four trials because individual data were not available from the authors. Within the remaining 28 trials, we excluded 11 patients due to missing information regarding patient age. Thus, our final analysis encompasses 9,421 individual patient records included in 28 RCTs.

Appendix 1, available in *Age and Ageing* online, gives an overview about the 28 included trials that were performed in 12 different countries, including Australia, Belgium, Brazil, China, Denmark, France, Germany, Italy, Serbia, Switzerland, the Netherlands and the USA. Thirteen trials were multicentric, 14 trials were performed in the ICU setting, 12 in the emergency department or medical ward and 2 were from primary care. The three largest trials were the SISPCT trial ($n = 1,089$) [11], the ProHOSP trial ($n = 1,359$) [24] and the SAPS trial ($n = 1,516$) [13]. All trials had a somewhat similar concept regarding the use of PCT with recommendations to initiate, continue or stop antibiotic treatment based on the PCT values on admission and during follow-up. Also, all trials have used highly sensitive PCT assays with a functional assay sensitivity of 0.06 µg/l (Kryptor PCT; Brahms, Hennigsdorf, Germany) and an assay time of less than 20 minutes to measure PCT in order to have optimal sensitivity and thus test performance. A detailed analysis regarding PCT algorithms used in the trials has been published previously [43].

Bias assessment regarding allocation concealment, blinded outcome assessment, number of patients with follow-up data for mortality and adherence to the PCT algorithm of the included trials is presented in Appendix 2, available in *Age and Ageing* online. Most trials had allocation concealment with central randomization and high follow-up for mortality. Only few trials had blinded outcome assessment. Adherence was variable among trials with 12 trials showing adherence to the PCT algorithm of more than 70% and 9 with lower than 70% (mostly ICU trials). In seven trials, adherence was not reported.

Baseline characteristics

Appendix 3, available in *Age and Ageing* online, shows baseline characteristics of included patients stratified according to randomization overall, and in the four age groups (<75 years [$n = 7,079$], 75–80 years [$n = 1,034$], 81–85 years [$n = 803$] and >85 years [$n = 505$]). Groups were well balanced regarding sociodemographic (age, gender), PCT levels, severity of illness and type of infection. The most common infection focus was the respiratory tract. Patients in the highest age group (>85 years) were less frequently included in ICU trials compared to younger patients.

Primary endpoint: duration of antibiotic treatment

Table 1 shows the primary endpoint (duration of antibiotic treatment) overall and again stratified by age groups and within subgroups. Overall, PCT-guided patients ($n = 4,714$) had a significantly lower mean duration of antibiotic treatment compared to control patients ($n = 4,707$) of 6.5 days versus 8.5 days (adjusted difference −2.01 days, [95% CI −2.32 to −1.69]). The effects of PCT use were different among different patient groups with more pronounced reduction of treatment duration in patients with respiratory tract infections, but the effects were similar among the different age groups overall (P for interaction 0.654) and

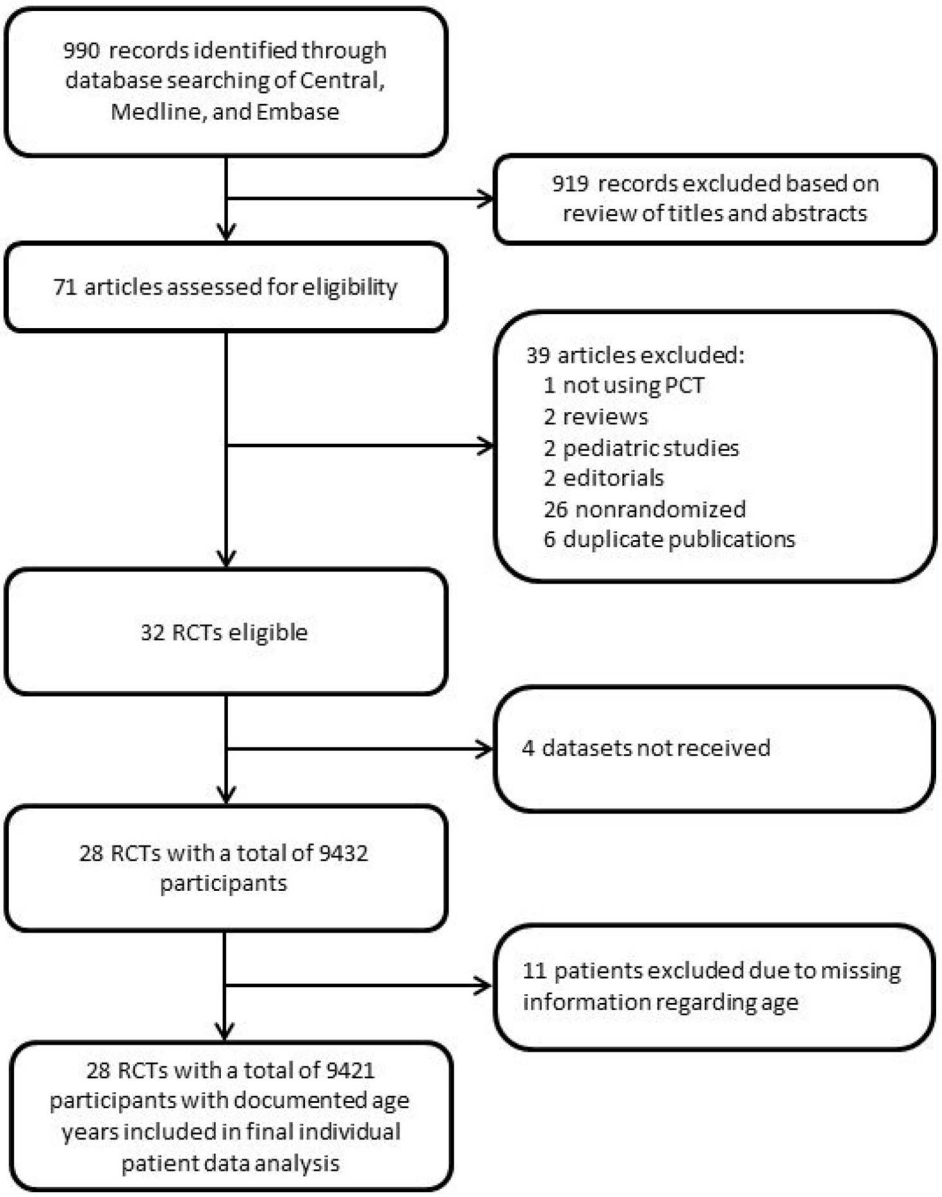

Figure 1. Study flowchart.

within the subgroups (Table 1 and Figure 2). As a sensitivity analysis, in a first step, we also included age as a continuous variable into the model and did not find evidence for effect modification of age on the association of PCT use and lower antibiotic treatment durations (*P* for interaction 0.644).

In a second step, we performed subgroup analysis of age to look for any old age-specific changes, which, however, also revealed to have no effect modification.

Secondary endpoint: mortality

Table 2 shows data about mortality overall, stratified by age group and stratified by age group within the different subgroups. Overall by 30 days, there were 543 deaths in 4,714 PCT-guided patients (11.5%) compared to 599 deaths in 4,707 control-group patients (12.7%), resulting in an adjusted OR for overall mortality of 0.90 (95% CI 0.81–1.00, $P = 0.046$). Effects on mortality were similar in all age groups with no evidence for effect modification (*P* for interaction 0.891) (Figure 3). The same was true also for all subgroups stratified by infection diagnosis, blood culture results, setting and sepsis severity. As a sensitivity analysis, we also included age as a continuous variable into the model and again did not find evidence for effect modification of age on the association of PCT use and mortality (*P* for interaction 0.507).

Secondary endpoint: length of stay

We found no significant difference regarding length of hospital stay as well as length of ICU stay in intervention compared to control group patients (overall 17.9 ± 23.5

Table 1. Primary endpoint (duration of antibiotic therapy [days]) overall and stratified by age, diagnosis, blood culture results, setting and sepsis severity

	Control (no. of Control group)	PCT (no. of PCT group)	Adjusted regression coefficient* (95% CI), *P* value	*P* for interaction
Antibiotic therapy [days], mean ± SD				
Subgroups by age				
Overall	(*n* = 4,707), 8.5 ± 8.2	(*n* = 4,714), 6.5 ± 7.8	−2.01 (−2.32, −1.69), *P* < 0.001	
Age <75 years	(*n* = 3,551), 8.4 ± 8.3	(*n* = 3,528), 6.4 ± 8.1	−1.99 (−2.36, −1.62), *P* < 0.001	0.654
Age 75–80 years	(*n* = 500), 9.2 ± 8.8	(*n* = 534), 7.2 ± 7.4	−1.98 (−2.94, −1.02), *P* < 0.001	
Age 80–85 years	(*n* = 405), 8.8 ± 7.0	(*n* = 398), 6.5 ± 7.1	−2.20 (−3.15, −1.25), *P* < 0.001	
Age >85 years	(*n* = 251), 8.6 ± 7.8	(*n* = 254), 6.5 ± 6.0	−2.10 (−3.29, −0.91), *P* < 0.001	
Subgroups by diagnosis				
Pneumonia				
Overall	(*n* = 974), 10.3 ± 5.7	(*n* = 962), 6.6 ± 5.1	−3.71 (−4.19, −3.24), *P* < 0.001	
Age <75 years	(*n* = 655), 10.2 ± 6.0	(*n* = 607), 6.3 ± 5.2	−3.89 (−4.51, −3.28), *P* < 0.001	0.555
Age 75–80 years	(*n* = 96), 10.9 ± 6.4	(*n* = 118), 7.5 ± 5.6	−3.51 (−5.13, −1.88), *P* < 0.001	
Age 80–85 years	(*n* = 117), 10.2 ± 4.0	(*n* = 114), 7.2 ± 4.9	−3.03 (−4.19, −1.87), *P* < 0.001	
Age >85 years	(*n* = 106), 10.4 ± 4.2	(*n* = 123), 6.5 ± 4.5	−3.86 (−5.01, −2.72), *P* < 0.001	
COPD/Bronchitis/upper ARI				
Overall	(*n* = 1,351), 4.6 ± 5.1	(*n* = 1,347), 2.3 ± 4.4	−2.32 (−2.68, −1.96), *P* < 0.001	
Age <75 years	(*n* = 1,067), 4.5 ± 4.7	(*n* = 1,067), 2.3 ± 4.4	−2.18 (−2.56, −1.81), *P* < 0.001	0.141
Age 75–80 years	(*n* = 122), 4.7 ± 6.2	(*n* = 123), 2.4 ± 3.8	−2.35 (−3.66, −1.05), *P* < 0.001	
Age 80–85 years	(*n* = 102), 6.1 ± 7.3	(*n* = 106), 2.2 ± 5.7	−3.79 (−5.59, −1.99), *P* < 0.001	
Age >85 years	(*n* = 60), 4.7 ± 4.9	(*n* = 51), 2.5 ± 3.6	−2.21 (−3.88, −0.53), *P* = 0.011	
Sepsis/septic shock				
Overall	(*n* = 2,382), 10.0 ± 9.7	(*n* = 2,405), 8.9 ± 9.1	−1.15 (−1.67, −0.63), *P* < 0.001	
Age <75 years	(*n* = 1829), 10.1 ± 9.7	(*n* = 1854), 8.9 ± 9.4	−1.19 (−1.79, −0.58), *P* < 0.001	0.546
Age 75–80 years	(*n* = 282), 10.6 ± 9.8	(*n* = 293), 9.1 ± 8.3	−1.36 (−2.84, 0.12), *P* = 0.072	
Age 80–85 years	(*n* = 186), 9.5 ± 7.9	(*n* = 178), 8.7 ± 7.9	−0.77 (−2.37, 0.84), *P* = 0.347	
Age >85 years	(*n* = 85), 9.1 ± 11.3	(*n* = 80), 9.0 ± 7.7	−0.46 (−3.39, 2.46), *P* = 0.755	
Subgroups by blood culture results				
Blood culture negative				
Overall	(*n* = 4,437), 8.1 ± 7.7	(*n* = 4,461), 6.2 ± 7.5	−1.92 (−2.23, −1.61), *P* < 0.001	
Age <75 years	(*n* = 3,365), 8.0 ± 7.8	(*n* = 3,356), 6.1 ± 7.7	−1.87 (−2.23, −1.5), *P* < 0.001	0.684
Age 75–80 years	(*n* = 467), 8.6 ± 7.9	(*n* = 494), 6.8 ± 7.2	−1.94 (−2.88, −1), *P* < 0.001	
Age 80–85 years	(*n* = 372), 8.4 ± 6.6	(*n* = 376), 6.2 ± 6.8	−2.12 (−3.06, −1.18), *P* < 0.001	
Age >85 years	(*n* = 233), 8.1 ± 5.9	(*n* = 235), 6.1 ± 5.6	−2.09 (−3.13, −1.05), *P* < 0.001	
Blood culture positive				
Overall	(*n* = 270), 15.6 ± 12.8	(*n* = 253), 12.7 ± 10.9	−2.92 (−4.97, −0.87), *P* = 0.005	
Age <75 years	(*n* = 186), 15.6 ± 12.1	(*n* = 172), 12.9 ± 11.8	−2.72 (−5.22, −0.21), *P* = 0.034	0.975
Age 75–80 years	(*n* = 33), 17.5 ± 14.9	(*n* = 40), 12.4 ± 8.8	−4.91 (−10.56, 0.74), *P* = 0.087	
Age 80–85 years	(*n* = 33), 13.9 ± 9.5	(*n* = 22), 12.6 ± 9.2	−1.25 (−6.59, 4.09), *P* = 0.641	
Age >85 years	(*n* = 18), 14.6 ± 19.5	(*n* = 19), 11.6 ± 8.1	−1.93 (−12.51, 8.64), *P* = 0.712	
Subgroups by setting				
Treatment in the ICU				
Overall	(*n* = 2,477), 9.7 ± 9.7	(*n* = 2,501), 8.6 ± 9.1	−1.11 (−1.61, −0.6), *P* < 0.001	
Age <75 years	(*n* = 1875), 9.8 ± 9.7	(*n* = 1911), 8.6 ± 9.4	−1.17 (−1.76, −0.58), *P* < 0.001	0.354
Age 75–80 years	(*n* = 306), 9.8 ± 9.8	(*n* = 310), 8.6 ± 8.3	−1.24 (−2.65, 0.16), *P* = 0.082	
Age 80–85 years	(*n* = 204), 8.7 ± 8.0	(*n* = 198), 7.8 ± 7.9	−0.79 (−2.26, 0.68), *P* = 0.29	
Age >85 years	(*n* = 92), 8.4 ± 11.2	(*n* = 82), 8.8 ± 7.7	−0.23 (−3.04, 2.59), *P* = 0.875	
Treatment in the medical ward				
Overall	(*n* = 1729), 8.1 ± 6.2	(*n* = 1706), 5.1 ± 5.4	−3.02 (−3.4, −2.63), *P* < 0.001	
Age <75 years	(*n* = 1,195), 7.8 ± 6.2	(*n* = 1,136), 4.9 ± 5.4	−2.89 (−3.36, −2.42), *P* < 0.001	0.242
Age 75–80 years	(*n* = 185), 8.4 ± 7.0	(*n* = 209), 5.5 ± 5.5	−3.03 (−4.26, −1.8), *P* < 0.001	
Age 80–85 years	(*n* = 194), 9.1 ± 5.9	(*n* = 191), 5.4 ± 6.0	−3.55 (−4.75, −2.36), *P* < 0.001	
Age >85 years	(*n* = 155), 8.8 ± 5.0	(*n* = 170), 5.4 ± 4.6	−3.44 (−4.49, −2.4), *P* < 0.001	
Primary care treatment				
Overall	(*n* = 501), 4.6 ± 4.1	(*n* = 507), 1.6 ± 3.2	−3.02 (−3.47, −2.57), *P* < 0.001	
Age <75 years	(*n* = 481), 4.6 ± 4.1	(*n* = 481), 1.6 ± 3.2	−2.97 (−3.44, −2.51), *P* < 0.001	0.611
Age 75–80 years	(*n* = 9), 6.4 ± 3.2	(*n* = 15), 1.9 ± 3.4	−4.58 (−7.49, −1.67), *P* = 0.004	
Age 80–85 years	(*n* = 7), 7.7 ± 4.2	(*n* = 9), 1.7 ± 2.5	−6.05 (−9.7, −2.4), *P* = 0.003	
Age >85 years	(*n* = 4), 3.0 ± 3.6	(*n* = 2), 3.5 ± 4.9	0.5 (−9, 10), *P* = 0.891	
Subgroups by organ failure				
SOFA 0–6				
Overall	(*n* = 3,747), 8.1 ± 8.0	(*n* = 3,783), 5.7 ± 7.2	−2.43 (−2.77, −2.09), *P* < 0.001	
Age <75 years	(*n* = 2,835), 7.9 ± 8.2	(*n* = 2,821), 5.5 ± 7.4	−2.41 (−2.82, −2.01), *P* < 0.001	0.93
Age 75–80 years	(*n* = 382), 8.7 ± 8.2	(*n* = 415), 6.4 ± 7.0	−2.6 (−3.64, −1.56), *P* < 0.001	
Age 80–85 years	(*n* = 319), 8.3 ± 6.6	(*n* = 321), 6.1 ± 7.2	−2.16 (−3.21, −1.11), *P* < 0.001	
Age >85 years	(*n* = 211), 8.9 ± 8.1	(*n* = 226), 6.2 ± 5.8	−2.74 (−4.04, −1.45), *P* < 0.001	
SOFA 7–9				
Overall	(*n* = 474), 10.1 ± 8.2	(*n* = 445), 10.2 ± 9.4	0.04 (−1.08, 1.15), *P* = 0.948	
Age <75 years	(*n* = 344), 9.9 ± 7.6	(*n* = 340), 10.4 ± 9.9	0.25 (−1.06, 1.57), *P* = 0.704	0.835
Age 75–80 years	(*n* = 62), 10.7 ± 11.4	(*n* = 55), 9.5 ± 7.0	−0.83 (−4.17, 2.5), *P* = 0.621	
Age 80–85 years	(*n* = 45), 11.4 ± 7.5	(*n* = 37), 9.3 ± 7.1	−1.95 (−5.27, 1.37), *P* = 0.245	
Age >85 years	(*n* = 23), 8.0 ± 7.4	(*n* = 13), 12.3 ± 8.1	6.36 (0.65, 12.06), *P* = 0.03	
SOFA 10–24				
Overall	(*n* = 486), 10.5 ± 9.1	(*n* = 486), 10.0 ± 8.8	−0.52 (−1.63, 0.59), *P* = 0.359	
Age <75 years	(*n* = 372), 10.8 ± 9.2	(*n* = 367), 10.3 ± 9.2	−0.57 (−1.88, 0.75), *P* = 0.398	0.872
Age 75–80 years	(*n* = 56), 10.7 ± 9.6	(*n* = 64), 10.9 ± 9.0	0.73 (−2.6, 4.07), *P* = 0.663	
Age 80–85 years	(*n* = 41), 10.1 ± 8.7	(*n* = 40), 7.7 ± 5.9	−1.72 (−4.98, 1.53), *P* = 0.294	
Age >85 years	(*n* = 17), 5.2 ± 3.8	(*n* = 15), 6.0 ± 3.9	0.99 (−1.94, 3.92), *P* = 0.494	

ARI, acute respiratory infection; COPD, chronic obstructive pulmonary disease. Values are presented as mean ± standard deviation. *Multivariable hierarchical regression with outcome of interest as dependent variable and trial as a random effect.

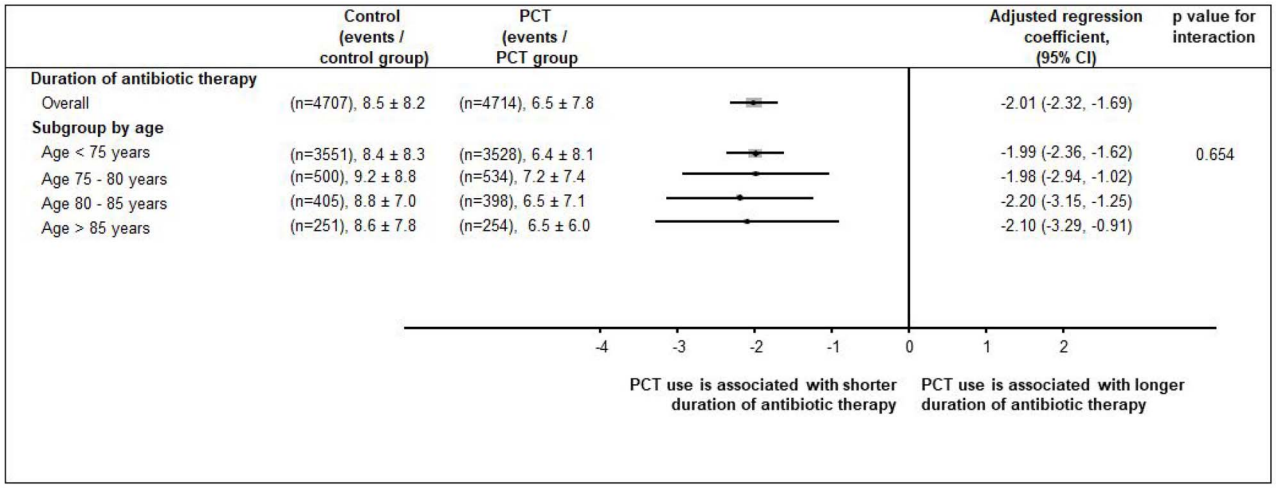

Figure 2. Forest plot showing duration of antibiotic therapy. Association of PCT-guided antibiotic stewardship and duration of antibiotic therapy in predefined subgroups. No., number.

versus 17.7 ± 23.7 days, adjusted difference 0.10, [95% CI −0.76 to 0.96], $P = 0.823$ and 13.5 ± 16.1 versus 13.6 ± 16.0 days, adjusted difference −0.01, [95% CI −0.88 to 0.86], $P = 0.983$) (Appendices 4 and 5). This finding was consistent throughout most subgroups without evidence for a subgroup effect (P for interaction ≥0.05 each), but there was evidence for a subgroup effect regarding length of ICU stay overall (P interaction = 0.014), in patients with septic shock (P interaction = 0.013), in patients with negative cultures (P interaction = 0.013), in ICU patients (P interaction = 0.013) and in patients with SOFA scores of 0–6 points (P interaction = 0.005).

Discussion

The main findings of this meta-analysis including individual patient data from 9,421 participants from 28 RCTs are 2-fold. First, regarding efficacy of PCT-guided antibiotic stewardship, we found a significant reduction of antibiotic exposure due to shorter antibiotic treatment durations in PCT-guided patients in all age groups and in all subgroups stratified by infection diagnosis, blood culture results, setting and sepsis severity. Second, regarding safety, our overall analysis showed a significant reduction in mortality in PCT-guided patients compared to control group patients with again no evidence for higher mortality based on age groups overall and within subgroups. Different subgroup analyses showed similar results. These data support the use of PCT also in the very old patient as an effective mean to lowering antibiotic exposure with no apparent harmful effects on mortality.

These data are reassuring as it remained unclear whether biomarkers of infection would have a similar clinical impact in older patients compared to younger patients due to known differences in the expression of cytokines resulting from bacterial infection [26, 27]. Thus, safety of using a biomarker for decision-making regarding antibiotic treatment in the very old patient population is paramount and has not yet been well documented as most previous RCTs did not focus on this specific patient population. Herein, our individual patient data meta-analysis provides important information in this regard.

Our analysis supporting the use of PCT in older patients is in line with several previous studies [44–46]. In a previous prospective observational study comparing different biomarkers and clinical signs in infected and uninfected patients in a geriatric teaching hospital in Switzerland, PCT was found to have high specificity towards infection but had an overall suboptimal performance [44]. Yet, due to the lack of a true reference standard for infection, the observational design may mask patients with true infection but negative cultures. Randomized research, however, may help to overcome this limitation by focusing on the effectiveness of the strategy regarding antibiotic consumption and clinical outcomes.

For this analysis, we pooled individual patient data from different trials. Trials differed in regard to the patient population (e.g. respiratory infection, general sepsis), setting (e.g. emergency room, medical ward, ICU) and type of PCT protocol used (e.g. recommendation regarding initiation versus stop of therapy) with also different cut-offs (e.g. 0.25 µg/l in lower risk settings versus 0.5 in higher risk settings). We have previously compared different PCT protocols and found PCT to be most helpful when used for early stopping antibiotic treatment, particularly in the setting of high patients such as patients with positive blood cultures, using the 0.25 µg/l cut-off for the emergency room setting and 0.5 µg/l for the ICU setting [43].

Adherence in trials was variable regarding following the PCT algorithm with lower adherence in ICU trials with higher risk patients. Interestingly, the difference in duration of antibiotic treatment between PCT-guided patients and control patients was lower in the ICU setting (−1.1 days)

Table 2. Secondary endpoint defined as mortality within 30 days overall and stratified by age, diagnosis, blood culture results, setting and sepsis severity

	Control (no. of events/no. of control group)	PCT (no. of events/no. of PCT group)	Adjusted OR* (95% CI), *P* value	*P* for interaction
30-day mortality, *n* (%)				
Subgroups by age				
Overall	599/4707 (12.7)	543/4714 (11.5)	0.90 (0.81, 1.00), *P* = 0.046	
Age < 75 years	378/3551 (10.6)	331/3528 (9.4)	0.87 (0.76, 1.00), *P* = 0.047	0.891
Age 75–80 years	93/500 (18.6)	89/534 (16.7)	0.86 (0.67, 1.10), *P* = 0.216	
Age 80–85 years	72/405 (17.8)	81/398 (20.4)	1.19 (0.91, 1.55), *P* = 0.211	
Age > 85 years	56/251 (22.3)	42/254 (16.5)	0.76 (0.55, 1.06), *P* = 0.104	
Subgroups by diagnosis				
Pneumonia				
Overall	49/974 (5.0)	45/962 (4.7)	0.92 (0.6, 1.39), *P* = 0.678	
Age <75 years	19/655 (2.9)	13/607 (2.1)	0.70 (0.34, 1.44), *P* = 0.337	0.833
Age 75–80 years	5/96 (5.2)	11/118 (9.3)	1.85 (0.61, 5.60), *P* = 0.276	
Age 80–85 years	13/117 (11.1)	10/114 (8.8)	0.81 (0.34, 1.96), *P* = 0.647	
Age >85 years	12/106 (11.3)	11/123 (8.9)	0.76 (0.32, 1.82), *P* = 0.538	
COPD/bronchitis/upper ARI				
Overall	18/1351 (1.3)	21/1347 (1.6)	1.21 (0.63, 2.29), *P* = 0.568	
Age <75 years	8/1067 (0.7)	9/1067 (0.8)	1.16 (0.44, 3.07), *P* = 0.768	0.634
Age 75–80 years	0/122 (0.0)	3/123 (2.4)	NA	
Age 80–85 years	3/102 (2.9)	4/106 (3.8)	1.29 (0.28, 5.97), *P* = 0.746	
Age >85 years	7/60 (12)	5/51 (10)	0.78 (0.23, 2.66), *P* = 0.694	
Sepsis/septic shock				
Overall	532/2382 (22.3)	477/2405 (19.8)	0.86 (0.75, 0.99), *P* = 0.038	
Age <75 years	351/1829 (19.2)	309/1854 (16.7)	0.85 (0.72, 1), *P* = 0.054	0.57
Age 75–80 years	88/282 (31.2)	75/293 (25.6)	0.73 (0.5, 1.05), *P* = 0.089	
Age 80–85 years	56/186 (30.1)	67/178 (37.6)	1.45 (0.93, 2.27), *P* = 0.102	
Age >85 years	37/85 (44)	26/80 (33)	0.63 (0.32, 1.23), *P* = 0.178	
Subgroups by blood culture results				
Blood culture negative				
Overall	546/4437 (12.3)	504/4461 (11.3)	0.91 (0.8, 1.03), *P* = 0.146	
Age <75 years	340/3365 (10.1)	308/3356 (9.2)	0.91 (0.77, 1.07), *P* = 0.268	0.947
Age 75–80 years	87/467 (18.6)	79/494 (16.0)	0.75 (0.53, 1.06), *P* = 0.104	
Age 80–85 years	66/372 (17.7)	77/376 (20.5)	1.24 (0.85, 1.79), *P* = 0.263	
Age >85 years	53/233 (22.7)	40/235 (17.0)	0.65 (0.41, 1.04), *P* = 0.07	
Blood culture positive				
Overall	53/270 (19.6)	39/253 (15.4)	0.7 (0.44, 1.11), *P* = 0.13	
Age <75 years	38/186 (20.4)	23/172 (13.4)	0.56 (0.31, 0.99), *P* = 0.046	0.519
Age 75–80 years	6/33 (18)	10/40 (25)	1.59 (0.49, 5.15), *P* = 0.438	
Age 80–85 years	6/33 (18)	4/22 (18)	0.68 (0.15, 3.11), *P* = 0.622	
Age >85 years	3/18 (17)	2/19 (11)	1.07 (0.13, 8.79), *P* = 0.952	
Subgroups by setting				
Treatment in the ICU				
Overall	532/2477 (21.5)	477/2501 (19.1)	0.86 (0.75, 0.99), *P* = 0.038	
Age <75 years	351/1875 (18.7)	309/1911 (16.2)	0.85 (0.71, 1), *P* = 0.051	0.430
Age 75–80 years	88/306 (28.8)	75/310 (24.2)	0.73 (0.5, 1.05), *P* = 0.092	
Age 80–85 years	56/204 (27.5)	67/198 (33.8)	1.36 (0.88, 2.09), *P* = 0.165	
Age >85 years	37/92 (40)	26/82 (32)	0.66 (0.34, 1.28), *P* = 0.218	
Treatment in the medical ward				
Overall	66/1729 (3.8)	66/1706 (3.9)	1.01 (0.71, 1.44), *P* = 0.937	
Age <75 years	27/1195 (2.3)	22/1136 (1.9)	0.85 (0.48, 1.5), *P* = 0.566	0.709
Age 75–80 years	5/185 (2.7)	14/209 (6.7)	2.49 (0.87, 7.18), *P* = 0.09	
Age 80–85 years	16/194 (8.2)	14/191 (7.3)	0.93 (0.44, 1.98), *P* = 0.854	
Age >85 years	18/155 (11.6)	16/170 (9.4)	0.77 (0.38, 1.58), *P* = 0.477	
Subgroups by organ failure				
SOFA 0–6				
Overall	303/3747 (8.1)	292/3783 (7.7)	0.95 (0.8, 1.12), *P* = 0.531	
Age <75 years	183/2835 (6.5)	166/2821 (5.9)	0.91 (0.73, 1.13), *P* = 0.406	0.862
Age 75–80 years	47/382 (12.3)	51/415 (12.3)	0.9 (0.59, 1.39), *P* = 0.648	
Age 80–85 years	39/319 (12.2)	45/321 (14.0)	1.22 (0.77, 1.95), *P* = 0.397	
Age >85 years	34/211 (16.1)	30/226 (13.3)	0.75 (0.43, 1.28), *P* = 0.285	
SOFA 7–9				
Overall	108/474 (22.8)	92/445 (20.7)	0.9 (0.65, 1.23), *P* = 0.504	
Age <75 years	62/344 (18.0)	62/40 (18.2)	1.06 (0.71, 1.56), *P* = 0.785	0.984
Age 75–80 years	25/62 (40)	12/55 (22)	0.4 (0.17, 0.92), *P* = 0.031	
Age 80–85 years	12/45 (27)	13/37 (35)	1.43 (0.54, 3.77), *P* = 0.469	
Age >85 years	9/23 (39)	5/13 (38)	1.25 (0.26, 5.96), *P* = 0.776	
SOFA 10–24				
Overall	188/486 (38.7)	159/486 (32.7)	0.77 (0.59, 1), *P* = 0.049	
Age <75 years	133/372 (35.8)	103/367 (28.1)	0.7 (0.51, 0.96), *P* = 0.026	0.684
Age 75–80 years	21/56 [38]	26/64 (41)	1.07 (0.5, 2.27), *P* = 0.858	
Age 80–85 years	21/41 (51)	23/40 (57)	1.14 (0.45, 2.89), *P* = 0.785	
Age >85 years	13/17 (76)	7/15 (47)	0.31 (0.07, 1.47), *P* = 0.14	

ARI, acute respiratory infection; COPD, chronic obstructive pulmonary disease; NA, not applicable. Values are presented as *n* (%). *Multivariable hierarchical regression with outcome of interest as dependent variable and trial as a random effect.

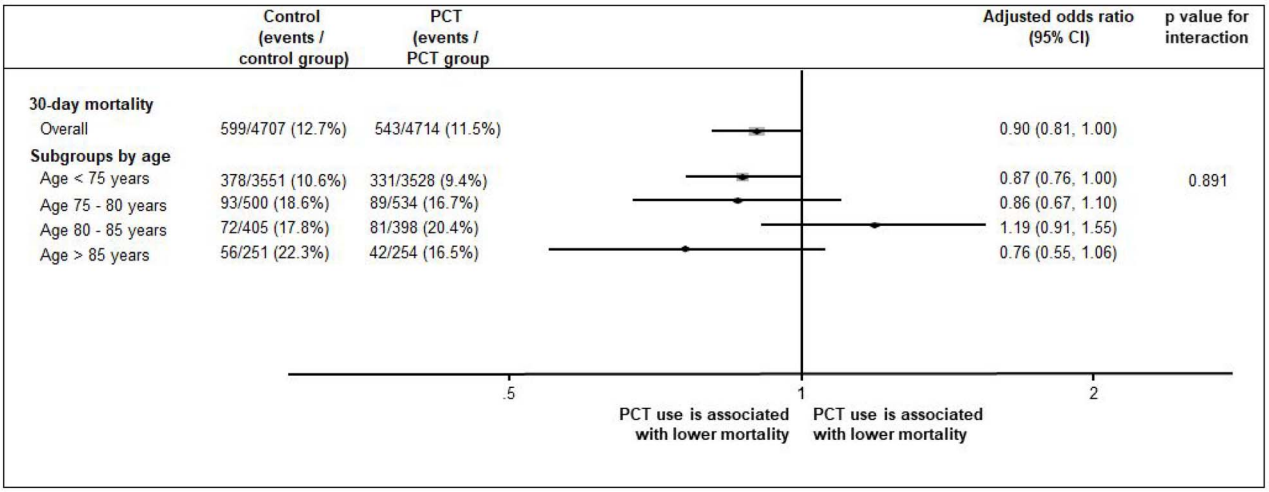

Figure 3. Forest plot showing 30-day mortality. Association of PCT-guided antibiotic stewardship and mortality in predefined subgroups. No., number.

compared to treatments in the medical ward (−3.0 days) or to the primary care treatment (−3.0 days). These differences may be explained by adherence to the PCT algorithm.

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 within different age group. There is some overlap with previous secondary reports from the same database particularly regarding description of trials and methodology used for analysis [21, 22, 28, 34, 35]. The focus on age groups regarding effects of PCT use, however, is novel and has not been done in previous reports. There are also some limitations to our study. First, we limited our data to immunocompetent adults and patients not being on haemodialysis before inclusion, thereby reducing generalizability of our conclusions to other patient populations. Also, typically, trial inclusion focuses on less severely ill old patients who will not die instantly thereby potentially neglecting older patients with higher severity of illness, again introducing selection bias. Second, the heterogeneity of our patient population with regard to focus of infection, clinical setting and disease severity also limits generalizability 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. Also, we had a limited number of patients in the oldest old age group, which was particularly true for the ICU setting. We also had very limited data on important prognostic factors such as nutrition and functional status, comorbidities and other heterogenic parameters of the oldest old population. Thus, specific trials in these particularly vulnerable patient populations are needed. Also, we had limited data on PCT kinetics and are thus not able to understand whether PCT levels behave differently according to age group of patients. Finally, this analysis is based on a systematic search and meta-analysis done in collaboration with Cochrane in 2017 and updated in February 2018, and more recent trials have not yet been included. An update of the overall analysis is planned in 2021 with results expected within 6–12 months. Most trials used the same PCT assay (Kryptor PCT; Brahms, Hennigsdorf, Germany), but today several other commercial PCT assay exist today with comparable results [47]. Finally, in our subgroup, analysis of age was based on chronological age and the use of biological age might would reveal different results.

Conclusions

In conclusion, this large individual patient data meta-analysis confirms that PCT-guided antibiotic treatment in older patients is associated with significantly reduced antibiotic exposures and no increase in mortality. Specific trials focusing on infections in the oldest old populations should be indorsed to safely reduce antibiotic consumptions in this particularly vulnerable population of patients.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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