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REVIEW

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The potential clinical value of pairing procalcitonin and lung ultrasonography to guide antibiotic therapy in patients with community-acquired pneumonia: a narrative review

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ABSTRACT

Introduction: Lower respiratory tract infections (LRTIs) are among the most frequent infections and are prone to inappropriate antibiotic treatments. This results from a limited accuracy of diagnostic tools in identifying bacterial pneumonia. Lung ultrasound (LUS) has excellent sensitivity and specificity in diagnosing pneumonia. Additionally, elevated procalcitonin (PCT) levels correlate with an increased likelihood of bacterial infection. LUS and PCT appear to be complementary in identifying patients with bacterial pneumonia who are likely to benefit from antibiotics.

Areas covered: This narrative review aims to summarize the current evidence for LUS to diagnose pneumonia, for PCT to guide antibiotic therapy and the clinical value of pairing both tools.

Expert opinion: LUS has excellent diagnostic accuracy for pneumonia in different settings, regardless of the examiner's experience. PCT guidance safely reduces antibiotic prescription in LRTIs. The combination of both tools has demonstrated an enhanced accuracy in the diagnosis of pneumonia, including CAP in the ED and VAP in the ICU, but randomized controlled studies need to validate the clinical impact of a combined approach.

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Antibiotic; community-acquired pneumonia; lower respiratory tract infection; lung ultrasound; procalcitonin; review

1. Introduction

Lower respiratory tract infections (LRTIs) such as bronchitis, exacerbated chronic obstructive pulmonary disease and community-acquired pneumonia (CAP) are among the most frequent infections and causes for antibiotic use. They are frequently overtreated with antibiotics due to lack of a diagnostic gold standard and difficulties in identifying bacterial pneumonia [1–6]. Chest X-ray (CXR) lacks accuracy and is often misinterpreted for the diagnosis of pneumonia. One of its limitations is overprojection of different structures, which complicates its interpretation. However, CXR is still considered the gold standard for LRTI imaging [7–11]. Chest computer tomography (CT) is considered more sensitive but is not possible in many settings due to limited availability, high cost, and has not been shown superior for patient management [10,12,13].

New diagnostic tools such as lung ultrasound (LUS) and procalcitonin (PCT) have the potential to overcome those challenges by increasing diagnostic accuracy to better guide antibiotic treatment. Lung ultrasound is an easy to learn widely available tool which has shown excellent sensitivity and specificity in diagnosing pneumonia [14,15]. A limitation of LUS results from interposition of air between the pleura and the consolidation in central pneumonia, which hinders its visibility. Nonetheless, central pneumonia is observed only in 1.5–10% of the patients [16]. Procalcitonin is a host biomarker which is released ubiquitously by parenchymal cells in response to microbial toxins and bacterial-specific proinflammatory mediators [17]. On the contrary, PCT secretion tends to be inhibited by cytokines produced in response to viral infection [18]. There is also a correlation between PCT levels and severity of bacterial infection [19–21]. LUS and PCT offer distinct advantages that complement each other in identifying patients with bacterial pneumonia who are likely to benefit from antibiotics.

This narrative review aims to analyze comprehensively, critically and objectively the current knowledge of the clinical value of pairing procalcitonin and lung ultrasonography to guide antibiotic therapy in patients with lower respiratory tract infections based on the available literature. We summarize the evidence behind the performance of LUS to diagnose CAP, behind the use of procalcitonin to guide antibiotic therapy and the clinical value of pairing both tools.

2. Methods

We conducted a systematic search, with the aid of a biomedical librarian, of (1) meta-analyses or systematic reviews of studies evaluating the performance of LUS to diagnose pneumonia and randomized controlled studies on the clinical impact of LUS to diagnose pneumonia; (2) meta-analyses of randomized controlled trials using PCT to guide

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Article highlights

- LUS has an excellent diagnostic accuracy for pneumonia in all health-care settings, both in the hands of experts and non-experts.
- No randomized studies have been performed to evaluate the impact of LUS on antibiotic prescription or on patients' outcomes
- PCT guidance reduces antibiotics initiation among adults with LRTI with no apparent adverse impact on disease course, length of stay or mortality and significantly reduces the risk for antibiotic-related side effects.
- Only few observational studies evaluated the combination of LUS and PCT and suggest an improved diagnostic accuracy with a combined approach.
- Clinical trials are needed to investigate the clinical impact of pairing both tools as well as its acceptability and feasibility.

antibiotic therapy in LRTIs; and (3) published studies (any type) pairing LUS and PCT to guide antibiotics prescription in LRTIs in Embase and Medline on May 15, 2023. Figure 1. shows the study selection process. We used a combination of controlled vocabulary of keywords around respiratory infections, ultrasound, and procalcitonin (See Search strategy in supplementary material). Only English-written articles were included. We did not limit our search to studies based on publication dates. We did not seek to identify research abstracts from meeting proceedings or unpublished studies as these are not commonly subjected to exhaustive peer-review. Giving its particular radiological presentation, we deliberately excluded studies focusing on SARS-CoV-2 infection.

3. Evidence behind the performance of LUS to diagnose CAP

A total of 259 studies were retrieved from database searching of Embase and Medline. After removal of duplicates, 44 articles were first selected on the basis of the titles or abstracts. Additional studies were then excluded because they were abstracts only ($n = 11$), focused on pulmonary disease or complications ($n = 3$), on neonatal respiratory distress syndrome ($n = 2$), on VAP ($n = 2$), letter to editor ($n = 1$), shortcut review ($n = 1$), on SARS-CoV-2 infection ($n = 1$), or asthma ($n = 1$). Finally, 21 meta-analyses or systematic reviews of studies evaluating the performance of LUS to diagnose CAP were included, and one randomized controlled trial on the clinical impact of LUS to diagnose pneumonia. Table 1 summarizes the characteristics of the meta-analyses and systematic reviews as well as the diagnostic performance of LUS for pneumonia in different settings and populations.

We found a wide range of studies investigating the diagnostic accuracy of LUS for pneumonia in different settings: primary care, emergency department (ED), hospitals and intensive care unit (ICU), and populations: adults or children. Ultra-sonographers had different levels of training and

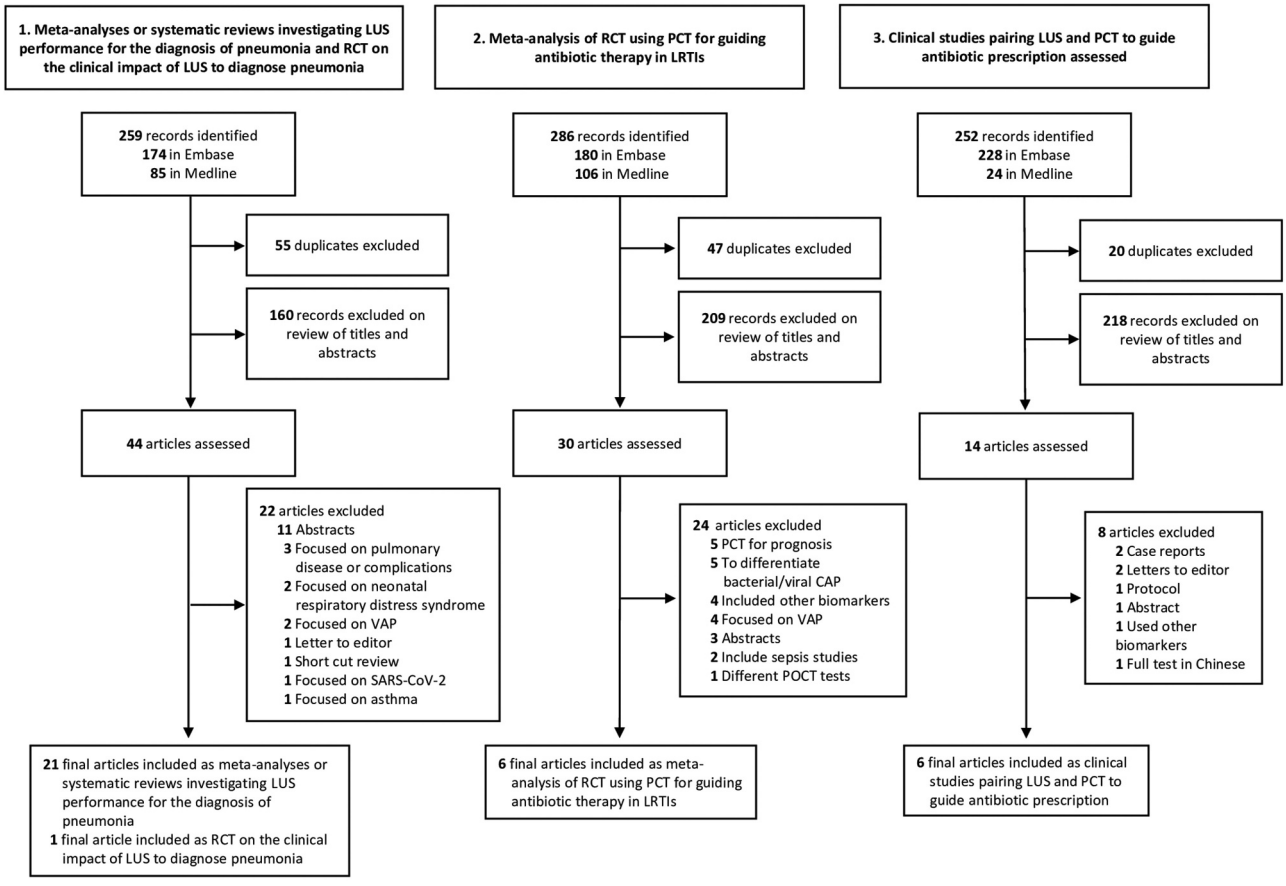

Figure 1. Study flow diagram. LUS: lung ultrasound, PCT: procalcitonin, LRTI: lower respiratory tract infection, RCT: randomized controlled trial, VAP: ventilator associated pneumonia, POCT: point of care test.

Table 1. Overview of meta-analyses and systematic reviews of studies evaluating the performance of LUS to diagnose pneumonia.

Author, year, ref	No. of studies included, country	No. of patients	Setting	Population: age	Reference standard	Pooled Se/Sp in %	Pooled PLR/NLR	AUROC	Experience of the ultra-sonographers Expert/non-expert
Chavez et al., 2014 [14]	10, Europe and China	1172	ED, Hosp, ICU	Adults ≥18 years	CXR, CT, Clinical	94/96	16.8/ 0.07	0.99	Experienced physicians or trained emergency physicians
Hu et al., 2014 [22]	9, Europe, USA., Egypt	1080	NA	NA	CXR, CT, Clinical	97/94	15.6/ 0.03	0.99	NA
Hew et al., 2015 [23]	4, Europe, Egypt	24	ICU	Adults ≥18 years	CT	NA	NA	NA	NA
Peredaet al., 2015 [24]	8. Europe, China, USA., Egypt	785	ED, Hosp ICU	Children age ≤ 18 years	CXR, Clinical	96/93	15.3/ 0.06	0.98	Physicians with different levels of expertise
Ye et al., 2015 [25]	5, Europe	742	NA	Adults	CXR, CT, Hospital discharge diagnosis	95/90	NA	0.90	Trained emergency physicians
Xia et al., 2016 [26]	14, Europe, China	1911	ED, Hosp ICU	Adults	CXR, CT, Clinical, Microbiological	90/88	6.6/0.08	0.96	Physicians with different level of expertise (from several hours' course to 10 years' practice)
Alzahrani et al, 2017 [27]	20, Europe, China, USA., Egypt	2513	ED, Hosp, ICU	Age: from 1 month to 100 years	CXR, CT, Clinical	85/93	11.1/ 0.08	0.98	Physicians with different level of expertise (experienced, trained physicians, residents with limited expertise, radiologists)
Llamas-Álvarez et al., 2017 [28]	16, Europe, Egypt, Iran, Turkey, China	2359	ED, Hosp, ICU	Adults aged ≥18 years	CXR, CT, Clinical	85/80	NA	0.93	NA
Long et al., 2017 [29]	12, Country NA	1515	NA	NA	CXR, CT	88/86	5.37/ 0.13	0.95	NA
Balk et al., 2018 [30]	12, Europe, Russia, Taiwan, USA, Turkey, India	1510	ED, Hosp	0–21 years	CXR, CT, Clinical	96/95	NA	NA	Trained residents with limited experience, and expert physicians
Orso et al., 2018 [31]	17, Country NA	2612	Outpatient, ED, Hosp, ICU	Children ≤18 years	CXR, CT, Clinical	94/93	NA	0.98	Physicians with from a 1-h training course up to 25 years of experience
Orso et al., 2018 [15]	17, Europe, USA, China, Turkey	5108	ED	Adults ≥18 years	CXR, CT, Clinical	97/92	NA	0.93	Emergency physicians (from 6 hours training to 10 years' experience)
Xin et al., 2018 [32]	8, Europe, USA, Taiwan	1013	ED, Hosp	Children <18 years	CXR and Clinical	93/96	25.8/ 0.07	0.98	Trained residents, pulmonologists, emergency physicians, and experienced physicians
Najgrodzka et al., 2019 [33]	22, Europe, USA, Egypt, Peru	3361	NA	Children <18 years	CXR, Clinical	93/92	NA	0.94	NA
Staub et al., 2019 [34]	14, Europe, China, Egypt, Iran, Turkey, Brazil, India, USA, Japan	1896	ED, ICU	Adults ≥16 years	CXR, CT, Clinical	90/83	NA	0.95	Trained emergency physicians, intensivist, radiologist or cardiologist
Tsou et al., 2019 [35]	25, Europe, Egypt, USA, China, Peru, Nepal Taiwan, India, Turkey	3353	Outpatient, ED, Hosp, ICU,	Children <21 years	CXR, CT, Clinical	94/92	12.4/ 0.07	0.97	Trained physicians to experienced radiologists
Wang et al., 2019 [36]	6, Europe, Turkey	701	ED	Children age < 18 years	Clinical, CT	97/87	8.1/0.05	0.99	Pediatricians or radiologists
Strom et al., 2020 [37]	17, Country NA	2170	ED, Hosp, ICU	Adults	CT, CXR, Clinical	NA	NA	NA	Physicians (from 1 h training to 10 years' experience)
Yan et al., 2020 [38]	22, Europe, USA, Taiwan, Egypt, China, Russia, Turkey, India, Australia	2470	ED, Hosp, ICU	Children <18 years	CXR, CT, Clinical	95/90	8.67/ 0.07	0.98	Experts and non-experts, including primary or temporary trainers
Sistani et al., 2021 [39],	16, Europe, Turkey, China, Nepal, Egypt, Kuwait, Iran	2040	ED, ICU	Adults ≥18 years	CT	96/85	9.74/ 0.05	0.98	Emergency physicians, intensivists or radiologists
Lu et al., 2022 [40]	29, Europe, Egypt, Mongolia, Turkey, Peru, India, USA., China	4565	Hosp, ED, ICU	Children <18 years	Clinical, CXR, CT	83/84	3.90/ 0.21	0.97	Trained physicians to expert radiologists

Abbreviations: AUROC: area under the receiver operating characteristic curve, CXR: chest X-ray, CT: computed tomography, ED: emergency department, Hosp: hospital, ICU: intensive care unit, NA: not available, NLR: negative likelihood ratio, PLR: positive likelihood ratio, ref: reference, Se: sensitivity, Sp: specificity.

expertise, ranging from a few hours of training to years of experience. The pooled LUS sensitivities and specificities to diagnose pneumonia ranged from 83% to 97% and from 80% to 96%, respectively. The pooled positive likelihood ratio (PLR) and negative likelihood ratio (NLR) ranged from 3.90 to 25.8 and from 0.03 to 0.21, respectively. The area under the receiver operating characteristic curve (AUROC) ranged from 0.90 to 0.99. This highlights that LUS has an excellent diagnostic accuracy for pneumonia in all settings and populations whether in the hands of expert and non-expert ultrasonographers and radiologists, other physicians or other health-care professionals. Studies covered a wide geographic range, but unfortunately, no data were available from sub-Saharan African countries. Studies employed varying definitions of pneumonia with respect to LUS patterns. These definitions spanned from the mere presence of consolidation to focal interstitial patterns (B-lines) and/or consolidation.

We only identified one randomized controlled study evaluating the impact of LUS on the management of pneumonia. Jones et al. [41] is a randomized control trial comparing LUS with CXR in 191 children from birth to 21 years of age suspected of having pneumonia in an ED. In the investigational arm, a LUS was performed and physicians had the option to perform CXR if there was clinical uncertainty after LUS. In the control arm a sequential imaging with CXR followed by LUS was performed. There was a 38.8% reduction (95% CI, 30.0%–48.9%) in CXR among investigational subjects. Novice and experienced physician-ultrasonographers achieved 30.0% (95% CI, 23.5%–36.5%) and 60.6% (95% CI, 47.0%–74.1%) reduction in CXR use, respectively. There were no cases of missed pneumonia among all study participants (investigational arm, 0.0%: 95% CI, 0.0%–2.9%; control arm, 0.0%: 95% CI, 0.0%–3.0%), or differences in adverse events, or subsequent unscheduled health-care visits between arms.

4. Evidence behind the use of PCT to guide antibiotic therapy in community-acquired LRTIs

A total of 286 studies were retrieved from database searching of Embase and Medline. After removal of duplicates, 30 articles were first selected on the basis of the titles or abstracts. Additional studies were then excluded because they investigated PCT for prognosis ($n = 5$), used PCT solely to differentiate bacterial to viral etiologies ($n = 5$), included other biomarkers ($n = 4$), focused on VAP ($n = 4$), were abstracts ($n = 3$), included sepsis studies or included different point of care tests (POCT, $n = 1$). Finally, six studies, including a total of 19,512 patients qualified as meta-analyses of randomized controlled trials using PCT to guide antibiotic therapy in community-acquired LRTIs and were included. Table 2 summarizes the characteristics of the studies as well as their main outcomes.

The meta-analysis by Li et al. [42] evaluated the impact of PCT-guided therapy on all-cause mortality, antibiotic use, and length of hospital stay in patients with LRTI. There was a significant reduction of antibiotic use in the PCT-guided group (RR 0.692, 95% CI: 0.55 to 0.88, $P = 0.03$) with no statistically significant differences for mortality (RR 0.998, 95% CI: 0.977 to 1.018) and length of stay (standardized mean difference: −0.355, $P = 0.097$).

The meta-analysis by Mathioudakis et al. [44] assessed the effectiveness of PCT-based protocols to guide the administration of antibiotics in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). They found that PCT-based protocols decreased antibiotic prescription with a relative risk (RR) of 0.56, (95% CI: 0.43 to 0.73) and total antibiotic exposure mean difference (MD) −3.83, (95% CI: −4.32 to − 3.35), without affecting clinical outcomes such as rate of treatment failure (RR 0.81, 95% CI: 0.62 to 1.06), length of hospitalization (MD − 0.76, 95% CI: −1.95– to 0.43), exacerbation recurrence rate (RR 0.96, 95% CI: 0.69 to 1.35) or mortality (RR 0.99, 95% CI: 0.58 to 1.69).

The meta-analysis by Hey et al. [45] evaluated the effectiveness and safety of PCT-guided antibiotic therapy in adults with LRTIs at primary care, ED and hospital level. All included studies used a cutoff PCT of 0.25 ng/mL, below which antibiotic treatment was discouraged. Some studies also used additional cutoffs <0.1 to strongly discourage and/or >0.5 ng/mL to strongly encourage antibiotic use. Their results demonstrated a statistically significant reduction in the odds of antibiotic initiation in the PCT-guided compared with standard care (OR = 0.26; 95% CI: 0.13–0.52; $p < 0.001$). Among studies that reported length of stay, there was no statistical differences between groups (8.02 vs 8.17 days in PCT-guided vs standard of care). There was no statistical difference on mortality in PCT-guided compared to standard of care (RR = 0.94, 95% CI: 0.69 to 1.28; $p = 0.957$).

The meta-analysis by Schuetz et al. [43] assessed the safety and efficacy of a PCT-algorithm over a large range of patients with varying levels of severity of LRTIs. The total antibiotic exposure per patient was significantly reduced overall, across all clinical settings and LRTIs diagnoses and was not associated with increased mortality or treatment failure. Subsequent meta-analyses by the same group [46,47] (same database reported in *Lancet Infect Dis*. 2018 and *Cochrane Database of Systematic Reviews* 2017) assessed the safety and efficacy of using PCT for starting or stopping antibiotics at primary care, ED and hospital level including ICU. PCT cutoffs for initiation of antibiotics were either 0.25 or 0.5 ng/mL. PCT cutoffs for discontinuation were <0.25, <0.5, <1, or a > 50–90% drop in PCT levels over time. PCT guidance was associated with a 2.4-day reduction in antibiotic exposure (5.7 vs 8.1 days; 95% CI −2.71 to −2.15; $p < 0.0001$) and a reduction in antibiotic-related side-effects (16% vs 22%, adjusted OR 0.68; 95% CI [0.57 to 0.82]; $p < 0.0001$). Mortality at 30 days was significantly lower in PCT-guided patients than in control patients: 286 (9%) deaths in 3336 PCT-guided patients vs 336 (10%) in 3372 controls; adjusted OR 0.83 (95% CI 0.70 to 0.99, $p = 0.037$).

All meta-analyses demonstrated that PCT is an effective and safe biomarker to reduce antibiotics exposure, with no apparent adverse impact on disease course, length of stay or mortality. Furthermore, it significantly reduces the risk for antibiotic-related side effects in the Schuetz et al. meta-

Table 2. Overview of meta-analysis of randomized controlled trial using PCT for guiding antibiotic therapy in community-acquired LRTIs.

Author, year, ref	No. of studies included, Country	No. of patients	Setting	Objective	Antibiotic initiation in PCT-guided vs. standard care OR or RR (95% CI)	Mortality in PCT-guided vs. standard care OR or RR (95% CI)	Length of hospital stay	AB related side effects OR (95% CI), *p* value
Li et al., 2011 [42]	8, Europe, USA	3431	NA	To evaluate the impact of PCT-guided therapy on all-cause mortality, antibiotic use, and length of hospital stay in patients with LTRI	**RR**: 0.692 (0.55–0.88), *P* = 0.03	**RR**: 0.998 (0.977–1.018)	**SMD**:-0.355, *P* = 0.097.	NA
Schuetz et al. 2012 [43]	14, Europa, USA, China	4221 Adults	Primary care, ED, Hosp, ICU	To assess the safety and efficacy of PCT-algorithm over a large range of patients with varying severity of LRTIs.	0.10 (0.07–0.14) *P* < .0001	0.94 (0.71–1.23)	Adjusted OR ED trials: −0.42 (−1.2–0.35) ICU trials: −1.36 (−4.5–1.77)	NA
Mathioudakis et al., 2016 [44]	8, Countries NA	1062	Hosp	To assess the effectiveness of PCT-based protocols to guide the administration of antibiotics in patients with AECOPD	**RR**: 0.56 (0.43–0.73)	**RR**: 0.99 (0.58–1.69)	**MD** −0.76, −1.95–0.43; I2=59%, moderate quality	NA
Hey et al., 2018 [45]	11, Countries NA	4090 Adults	Primary care, ED, Hosp	To evaluate the effectiveness and safety of PCT in guiding AB therapy in LRTI	0.26 (0.13–0.52)	0.93 (0.67–1.28)	**WMD**: −0.15 days (−0.60–0.30) *p* = 0.507	NA
Schuetz et al., 2019 [46,47]	26, Europe, USA, Brazil, China, Australia	6708 Adults	Primary care, ED, medical wards, ICU.	To assess the safety and efficacy of using PCT for starting or stopping antibiotics over a large range of patients with varying severity of ARIs and from different clinical settings	0.27 (0.24–0.32)	0.83 (0.7–0.99), *p*=0.037	−0.19 (−0.96 to 0.58), *p*=0.626	0.68 (0.57 to 0.82), *p*<0.0001

Abbreviations: AECOPD: acute exacerbation of chronic obstructive bronchitis, ARI: acute respiratory infection, ED: emergency department, Hosp: hospital, ICU: intensive care unit, MD: mean difference, NA: not available, OR: odds ratio, SMD: standardized mean difference, ref: reference, RR: risk ratio, WMD: weighted mean difference.

analysis [46,47]. Unfortunately, there are no data available including African countries and further studies are needed in that setting.

5. Evidence of the clinical value of pairing both LUS and PCT to guide antibiotic therapy in LRTI

A total of 252 studies were retrieved from database searching of Embase and Medline. After removal of duplicates, 14 articles were first selected on the basis of the titles or abstracts. Additional studies were then excluded because they were case reports ($n = 2$), letters to editors ($n = 2$), protocol ($n = 1$), abstracts ($n = 1$), used other biomarkers ($n = 3$) or full text was only available in Chinese ($n = 1$). Finally, six studies with a total of 1198 patients were selected. Five studies assessed the diagnostic accuracy of pairing LUS and PCT in the context of pneumonia. Only one study used an algorithm combining LUS and PCT to guide antibiotic prescription. The characteristics of the studies are listed in Table 3.

The population included in the different studies is heterogeneous and difficult to standardize. Five of the studies were conducted in the ICU, four including adults with suspected or confirmed VAP and one for children below 18 years with suspected CAP or nosocomial pneumonia acquired during their ICU stay. One study was carried out in the ED and another in ambulatory general practice including community-acquired LRTIs.

Zagli et al. [48] published a retrospective study in ICU-admitted adults with suspected VAP, testing the diagnostic accuracy of a new clinical score (CEPPIS score) including clinical infection signs, LUS, and PCT levels. A CEPPIS score >5 was found to be a good predictor of VAP, with an AUROC of 0.83.

Nazerian et al. [49] reported a prospective observational study evaluating the diagnostic accuracy of the combination of LUS with PCT for CAP among adults with respiratory complaints in the ED. The diagnosis of pneumonia was determined by independent clinicians based on all clinical data plus chest CT results. PCT was used to rule-out (if <0.25 ng/ml) or rule-in (if >0.5 ng/ml) pneumonia. The diagnostic accuracy, sensitivity, and negative predictive value of LUS/PCT (consolidation on LUS or PCT ≥0.25 ng/ml) were 88.8%, 96.7%, and 94.7%, respectively, for the diagnosis of pneumonia. Sensitivity of the LUS/PCT (≥0.25 ng/ml) was superior to CXR/PCT (≥0.25 ng/ml) (80.3%), to LUS alone (85.2%) and PCT alone (≥0.25 ng/ml) (73.8%). Specificity and positive predictive value of the combination of positivity of LUS and PCT (PCT >0.5 ng/ml) were 94% and 83.3%, respectively. The combination of LUS and PCT had the highest diagnostic accuracy of tested modalities.

Zhou et al. [50] published a prospective observational study to evaluate the diagnostic performance of the combination of LUS with PCT in mechanically ventilated patients who had symptoms suggestive of pneumonia. Positive LUS combined with a PCT of ≥0.25 ng/mL had a sensitivity of

Table 3. Overview of clinical studies pairing LUS and PCT to guide antibiotic prescription. ED: emergency department, ICU: intensive care unit, ref: reference, NA: not available, OR: odd ratio.

Author, year, country, ref	Study type	Setting	Population	No. of patients	Intervention	Outcome	Key result
Zagli, 2014, Italy [48]	Retrospective observational study	ICU	Adults with suspicion of VAP	221	No intervention	Diagnostic accuracy of the CEPPIS score (including clinical infection signs, LUS, and PCT levels), in identifying VAP using clinical signs, CXR and tracheal aspirate cultures as the reference standard.	AUROC showed a significantly higher diagnostic discriminative value for CEPPIS ≥5 than CPIS ≥6 (0.829 vs 0.616, respectively; $P< .0001$).
Nazerian et al., 2016, Italy [49]	Prospective observational study	ED	Adults with at least one unexplained respiratory complaint and a chest CT	128	No intervention	Diagnostic accuracy of the combination of LUS with PCT using the diagnosis of independent clinicians (based on clinical chart review including CT results) as the reference standard	Positive LUS or PCT >0.25: Sensitivity 96.7%, specificity 53.7%, LR+ 2.09, LR- 0.06
Zhou et al, 2019, China [50]	Prospective accuracy study	ICU	Adult with suspicion of VAP	124	No intervention	Diagnostic performance of the combination of LUS with PCT using CT and lower respiratory tract sample culture as the reference standard	Positive LUS and PCT >0.25: sensitivity 81.3%, specificity 85.5%, LR+ 0.22
Lhopitallier et al., 2021, Switzerland [51]	Three group pragmatic cluster randomized controlled trial	Primary care	Adult with a clinical suspicion of pneumonia	469	PCT guided AB versus PCT + LUS (only in case of high PCT) guided AB	Antibiotic prescription by day 28, duration of restricted activities within 14 days	No significant difference in probability of antibiotic prescription between PCT + LUS and PCT alone groups (0.41 *v* 0.40, −0.03 (−0.17 to 0.12)). No difference in duration of restricted activities: 0.0 days (95% CI −1.48 to 1.43)
Guitart et al., 2022, Spain [52]	Prospective blinded cohort study	ICU	Children <18 years with suspected CAP or with suspected nosocomial pneumonia	194	No intervention	- Diagnostic accuracy of LUS and PCT versus CXR and PCT for BP diagnosis - Concordance between the final diagnosis made by an expert and the diagnosis determined by LUS plus PCT or CXR plus PCT, for bacterial pneumonia and viral pneumonia	LUS and PCT sensitivity 90%, specificity 85%, PPV 88, NPV 88
Ammar et al., 2022, Egypt [53]	Prospective blinded cohort study	ICU	Adults with a confirmed diagnosis of VAP by positive sputum culture	62	No intervention	Correlation between LUS reaeration score and PCT levels after 7 days of antibiotics	The LUS reaeration score showed a highly significant negative correlation with PCT on day 7 (-0.718, $p < 0.001$). A cut-off of 5 for the LUS score showed a sensitivity of 92.5%, specificity of 95.5%, positive predictive value of 97.4% and negative predictive value of 87.5% in detecting a low PCT score on day 7

Abbreviations: ED: emergency department, ICU: intensive care unit, ref: reference, NA: not available, OR: odds ratio.

81.3% and specificity of 85.5% in diagnosing VAP, which was defined based on a combination of chest CT and semi-quantitative bacterial culture of bronchial suctioning or bronchoscopic lavage. The AUROC was significantly higher for LUS combined with PCT (0.865) than for a white blood cell count, PCT, C-reactive protein, or Clinical Pulmonary Infection Score alone.

Lhopitalier et al. [51] performed a three group pragmatic cluster randomized controlled trial evaluating an algorithm with sequential combination of PCT and LUS (recommended only in patients with PCT ≥ 0.25) to reduce antibiotic prescription compared with either PCT only or usual care. The study population included patients consulting general practitioners for a LRTI. Results demonstrated that point-of-care PCT led to a 26% absolute reduction in the probability of 28-day antibiotic prescription without affecting patients' safety. However, LUS did not further reduce antibiotic prescription, when done in patients with elevated PCT.

Guitart et al. [52] published a randomized, blinded, controlled clinical trial comparing the diagnostic accuracy of LUS and PCT versus CXR and PCT for the diagnosis of bacterial pneumonia. A PCT value ≥1 ng/ml was considered to indicate bacterial infection. The study populations were children <18 years old with suspected CAP requiring ICU admission or children with suspected nosocomial pneumonia acquired during their ICU stay. The results showed a sensitivity and specificity respectively of 90% (95% CI: 83–94) and 85% (95% CI: 76–91) when combining LUS and PCT and of 95% (95% CI: 90–98) and 41% (95% CI:

31–52) when combining CXR and PCT. The positive predictive value for LUS and PCT was higher (88%, 95% CI 79%–93%) than for CXR and PCT (68%, 95% CI: 60%–75%, $p < 0.001$).

Ammar et al. [53] performed a prospective blinded cohort study assessing the correlation between a LUS reaeration score and PCT levels to discontinue antibiotic therapy in ICU patients with VAP after 7 days of antibiotics. The LUS reaeration score showed a significant negative correlation with PCT on day 7 (-0.718, $p < 0.001$). A LUS score of 5 points, which indicated a change from consolidation to normal aeration, showed a sensitivity of 92.5%, specificity of 95.5%, positive predictive value of 97.4% and negative predictive value of 87.5% in detecting a low PCT score on day 7.

We also searched for ongoing clinical trials pairing LUS and PCT to guide antibiotic prescription in LRTIs, in ClinicalTrials.gov, clinicaltrialsregister.eu and the International Clinical Trials Registery Platform of the World Health Organization. Only one ongoing clinical trial was identified: the PLUS-IS-LESS study, trial registration: NCT05463406. It is a pragmatic stepped-wedge cluster-randomized controlled clinical trial, conducted in nine Swiss EDs assessing an algorithm combining a clinical score, LUS, PCT, and a clinical severity score for the management of LRTIs in adults, compared with usual care. The co-primary outcomes are the proportion of patients with clinical failure and the proportion of patients prescribed an antibiotic in each group between enrollment and day 28.

6. Conclusion

The evidence demonstrates that LUS is a very accurate tool for diagnosing CAP in all settings and in the hands of experts and trained non-experts. All meta-analyses found that PCT is an effective and safe biomarker to reduce antibiotic exposure, with no apparent adverse impact on length of stay or mortality in community-acquired LRTIs. Pairing both tools has shown to increase the accuracy for diagnosing pneumonia, CAP in the ED and VAP in the ICU. This highlights the potential of algorithms based on LUS and PCT to optimize antibiotic therapy and fight antimicrobial resistance. The only available randomized controlled study using an algorithm pairing both tool was performed in the primary care setting did not show any advantage of combining PCT and LUS over using PCT alone on antibiotic prescription. However, LUS was only recommended in patients with elevated PCT and most patients had a low PCT. This result highlights the importance of identifying the optimal way of combining PCT and LUS to guide prescription of antibiotics and get a maximal benefit from their complementarity. As today, there is no evidence of a positive impact of a combined PCT and LUS approach and randomized controlled studies have to be conducted.

7. Expert opinion

LTRIs are among the most common infections and stand as the leading cause of inappropriate antibiotic prescription [4]. Antibiotic misuse contributes to selection of antibiotic resistance, which is a major public-health threat of our century. There is significant room for improvement of the diagnostic tools in order to better identify patients who will most likely benefit from antibiotics.

As described in this review, LUS has proven better diagnostic performance than CXR in many studies and in a wide range of setting. Some guidelines already suggest LUS as an alternative to CXR for the management of patients with suspected pneumonia [11,54]. However, no randomized studies have been performed to evaluate the impact of LUS on antibiotic prescription or on patients' outcomes [55]. PCT has shown to safely reduce antibiotic prescription in patients with LRTIs. It is very likely that a combination of those two tools can further reduce antibiotic misuse while ensuring patients' safety. The way of combining PCT and LUS needs to be tailored to the level of care (primary care, ED, ICU) and the severity of LRTI. Indeed, a combination with high sensitivity to detect pneumonia is of prime importance in the ED and ICU to ensure the safety of patients with severe infections, while a combination with high specificity is needed in primary care where most patients have a non-severe LRTI and do not need antibiotic treatment. Clinical trials need to be done to investigate the clinical impact of pairing both tools as well as its acceptability and feasibility before larger implementation.

7.1. Five-year view

Ultrasound machines have evolved over the last decade with substantial improvement of the image quality and hardware miniaturization. Currently, different pocket-size devices are available and have been validated in clinical practice. Indeed, hand-carried devices have reached good-quality images, comparable to traditional echographic machines [56,57]. There is growing interest and enthusiasm in ultrasound and more and more physicians are getting trained. It is easy to learn, rapidly performed, low-cost, and has shown to shorten time to diagnosis [58]. It is likely that the use of LUS will gradually replace CXR as the first imaging tool for pneumonia diagnosis.

The use of biomarkers of inflammation to guide clinicians in prescribing antibiotics in patients with LRTIs has been investigated in many studies. PCT is among the most studied, and its use is validated to guide and/or monitor treatment in pneumonia by several guidelines [54,59]. LUS and PCT-based algorithms to guide antibiotic prescription in LRTIs are a promising approach to optimized antibiotic therapy and fight increasing antimicrobial resistance.

Declaration of interests

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