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Inflammatory biomarker-based clinical practice in patients with pneumonia: A systematic review of randomized controlled trials

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Abstract

Objectives: Biomarker-based clinical practice is currently gaining ground and increasingly affects decision making. A variety of biomarkers have been studied through the years and some of them have already an established role in modern medicine, such as procalcitonin (PCT) which has been proposed to reduce antibiotic exposure. We purposed to systematically review all biomarkers examined for guiding the clinical practice in patients with pneumonia.

Methods: A systematic review on PubMed was performed on April 2023 by two independent researchers using the PRISMA guidelines. Randomized trials which enrolled patients with pneumonia and compared biomarker-guided strategies to standard of care were included.

Results: 1242 studies were recorded, from whom 16 were eligible for this study. 14 studies investigated PCT as a biomarker. From these, 8 studies reported on community acquired pneumonia (CAP), 2 on ventilator associated pneumonia (VAP), 1 on aspiration pneumonia, 1 on hospital acquired pneumonia (HAP) and 2 on exacerbation of chronic obstructive pulmonary disease (ECOPD). There was 1 study, referred to VAP, that investigated interleukin-1β (IL-1β) and interleukin-8 (IL-8) and 1 study that reported the role of C-reactive protein (CRP) in ECOPD. In a total of 4751 patients in 15 studies, the biomarker-based approach did not lead to increased mortality [OR: 0.998 (95%CI: 0.74–1.34, p value: 0.991). I2:19%]. Among different types of pneumonia and time-points of assessment, biomarker-guided practice appeared to improve antibiotic-related outcomes, such as rate of antibiotic prescription, duration of antibiotic therapy and rate of antibiotic exposure, while 5 studies reported a possible decrease in antibiotic-related adverse effects. Biomarker-guided practice did not seem to lead in an increase in other adverse outcomes such as need for hospitalization and duration of hospitalization. However, the included studies have high risk of bias mainly due to improper blinding of participants/personnel and outcome assessors.

Conclusion: Biomarker-guided clinical practice improves provided healthcare, in terms of reduced antibiotic consumption with no inferiority to mortality, relapses and exacerbations in patients with different types of pneumonia. Thus, such approaches should be further evaluated to achieve personalized medicine.

Keywords: randomized controlled trials, biomarkers, precision medicine, pneumonia.

What is new? What is important?

- The majority of clinical trials in adults with pneumonia evaluated the use of procalcitonin.
- Biomarker-guided clinical practice may optimize antibiotic usage without increasing mortality or treatment failure.
- Future research should expand to novel biomarkers and vulnerable populations, such as elderly and immunocompromised individuals.
- In this field, effort should be put into reducing risk of bias stemming from improper blinding of practitioners and outcome assessors.

INTRODUCTION

Pneumonia is a major cause of hospitalization, mortality, and morbidity around the word. According to the clinical and epidemiological characteristics, patients with pneumonia can be furtherly separate to facilitate better clinical approach. For example, community-acquired pneumonia is usually caused by *Streptococcus pneumoniae, Haemofilus influenzae, Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (among others) [1], while Ventilator-Associated Pneumonia (VAP) can be furtherly caused by Methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacilli [2].

As medical community tries to approach precision and patient-centered medicine, an increasing number of biomarkers are used in clinical practice. CRP and procalcitonin have been assessed and used for decades, but novel inflammatory biomarkers have also been proposed [3]. Although there seems to be a large number of observational studies reporting on between-group differences, prognostic and diagnostic accuracy, widespread use of inflammatory biomarkers cannot be achieved without pivotal clinical trials that would prove the superiority of biomarker-based clinical practice.

The aim of this systematic review is to assess the available evidence on the effectiveness of biomarker-based clinical practice vs usual clinical practice on meaningful clinical outcomes in patients with pneumonia.

MATERIAL AND METHODS

The protocol for this systematic review has been registered at PROSPERO (CRD42023431116).

SELECTION AND DATA COLLECTION PROCESS

After removing duplicates, each study was screened by two independent authors (DD, MK), while conflicts were resolved by a third author (TP).

For each study the follow data were extracted: first author, year of publication, population, interventions, comparison, setting, type of lower respiratory tract infection, main and secondary outcomes and effect sizes. Additionally, for each study we collected information needed to make risk of bias judgements.

SEARCH AND ELIGIBILITY CRITERIA

We conducted a systematic search in PubMed on April 2023 using relevant terms of commonly used biomarkers based on our previous experience and research. The full search strategy can be found in the Appendix (Supplementary material). Previous reviews on this topic and trial registries were evaluated for additional eligible articles.

Patients: We included studies evaluating the effect of biomarker-based practice in adult patients with pneumonia, without restriction to setting or severity (e.g. community-acquired pneumonia, hospital-acquired pneumonia, ventilator associated pneumonia, aspiration pneumonia).

Interventions: Relevant interventions were considered those that made clinical decisions (e.g. discontinuation of antibiotic treatment, hospital admission) based on the measurement of inflammatory biomarkers. For a detailed but not exhaustive list of the eligible biomarkers, see search strategy.

Comparator: Studies that compared biomarker-based practice to common clinical practice were eligible for inclusion in our review.

Study Design: We included randomized clinical trials as we were interested in the effectiveness of the intervention.

STUDY RISK OF BIAS ASSESSMENT

Risk of Bias assessment was performed independently by two authors using the Cochrane ROB tool. The following domains were assessed:

1. Sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective reporting (reporting bias).
7. Any other bias.

DATA SYNTHESIS

Random effects meta-analysis was performed for our main outcome of mortality. For our secondary outcomes, narrative synthesis was chosen due to the broad scope and high expected heterogeneity in the reported outcomes in the included studies. We categorized studies by type of infection (VAP, HAP etc.), as this categorization adequately reflects the underlying populations of interest. Harvest plots were used to visualize our findings.

RESULTS

The identified references from PubMed were 1242. After screening of abstracts was performed, 1224 references were excluded, and 18 references were further investigated for inclusion by reading the full texts. 12 studies were finally eligible for inclusion and 5 reports were excluded. From these 5 reports, 1 study (Bobylev AA 2019) [4] was excluded because the full text was found only in Russian, 1 study (Barak-Corren Y 2021) [5] was excluded because it was referring to pediatric patients and 1 study (Ulm L 2017) [6] was excluded because it investigated the PCT guided therapy in patients after stroke. The 2 remaining reports were excluded because they were protocols. The studies of these protocols were finally found from other sources. Studies from other sources were Hellyer 2019 [7], Christofer Butler 2019 [8], Stolz D. 2007 [9] and Matthias Briel 2008 [10] (Fig. 1).

The included studies were further classified into five groups according to the type of pneumonia to which they referred (CAP, VAP, HAP, ECOPD and aspiration pneumonia).

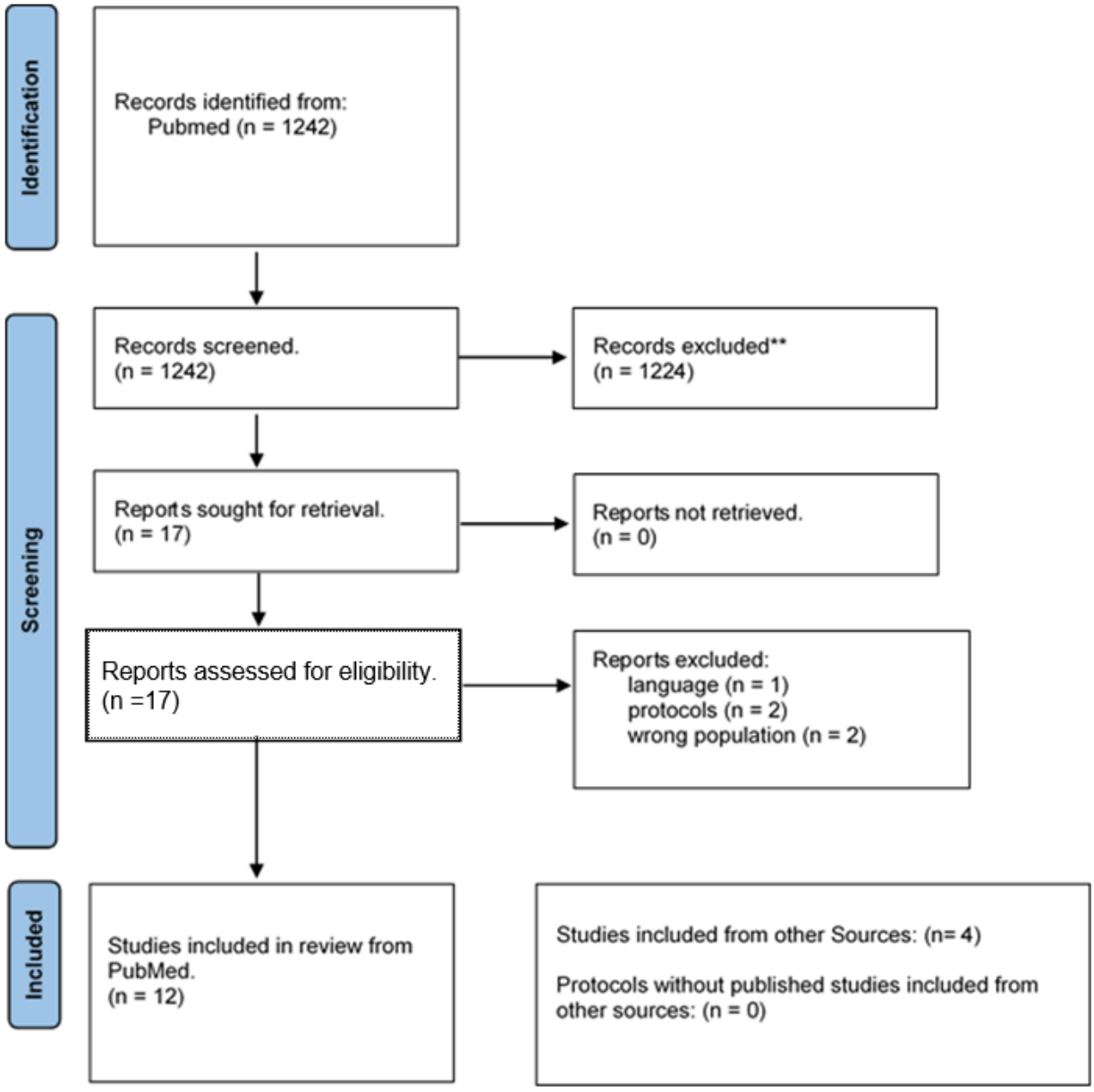


Figure 1. Flow Diagram.

CAP (COMMUNITY ACQUIRED PNEUMONIA)

Regarding community-acquired pneumonia, 8 studies were classified in this group and all of them used procalcitonin. In this category there were 4 studies that reported suspected CAP:

Lhopitallier L. *et al.* [11] conducted an open label cluster randomized trial in which randomization was performed at general practitioner level. Antibiotics prescription was guided by PCT (n = 195) or PCT + Ultrasound (UltraPro) (n = 152) compared to standard of care (n = 122). Compared to the standard of care group, the probability of **antibiotic prescription** by day 28 was lower in the procalcitonin group (0.40 v 0.70, cluster corrected difference −0.26) (95% CI:−0.41 to −0.10) and no significant difference in antibiotic prescription by day 28 between the UltraPro group and procalcitonin group was observed (0.41 v 0.40, −0.03 (95% CI:−0.17 to 0.12)). The **median number of days with restricted activities** due to lower respiratory tract infection by day 14 was 4 days in the procalcitonin group and 3 days in the usual care group. while there was no difference in this outcome between the UltraPro and procalcitonin groups.

Montassier E. *et al.* [12] reported, in an open-label multicenter randomized clinical trial in which patients received either PCT guided initiation of antibiotic therapy and discontinuation (n = 142) or usual care (n = 143), that **antibiotic duration** was not significantly different between the clinical assessment and procalcitonin-guided groups (median 9 days [IQR range 6 to 13 days; range 0 to 30 days] versus 10 days [IQR 7 to 14 days; range 1 to 29 days], respectively; p=0.21). Significantly more participants received antibiotic treatment for less than or equal to 5 days in the clinical assessment group compared with the procalcitonin group (32 [24%] versus 19 [14%], respectively; difference 10%; 95% CI 6% to 17%). **Clinical success** rate was 92% in both groups and serious adverse outcome rates were similar.

The study by Mirjam Christ-Crain *et al.* [13] was an open-label interventional study. In the experimental group (n=151), PCT was used to determine the initiation and the duration of antibiotic therapy, while in the control group (n=151) patients received antibiotics according to usual practice. Procalcitonin guidance reduced total **antibiotic exposure** (relative risk, 0.52; 95% confidence interval, 0.48–0.55; p < 0.001), **antibiotic prescriptions** on admission (85 vs. 99%; p < 0.001), and **antibiotic treatment duration** (median, 5 vs. 12 d; p < 0.001) compared with control group. In both groups, laboratory and clinical measures of outcome were similar at baseline, during the early course of the disease (Days 4, 6, and 8) and at follow-up after a mean of 6.9 ± 1.9 weeks.

The publication by Wussler D *et al.* [14] reported the results of two distinct studies. At first, a multicenter diagnostic study and secondly, a randomized management study of procalcitonin guidance in patients with acute heart failure and suspected pneumonia. In the management study, in the PCT group (n=25) the duration of antibiotic therapy was determined by PCT measurements. The control group (n=20) received usual care. The management study was stopped early due to the unexpectedly low AUC of procalcitonin in the diagnostic study. Interestingly, in the second study **the duration of antibiotic treatment** was similar in both groups (PCT 10.5 (6.0–12.2) days and control 10.5 (8.8–13.2), p value 0,39). The length of hospital stay was also similar (PCT 10.0 (6.0–18.2) days and control 14.0 (6.8–24.2) days, P value 0,39).

We also found 1 study investigating low risk CAP according to Pneumonia Severity Index (PSI):

The study by Long W. *et al.* [16] was a randomized controlled trial including 172 patients with low-risk CAP between 18-65 years and PSI class I–III, which assessed the value of PCT-guided antibiotic discontinuation strategy (PCT group n=86) compared to control group (n=86). The total rate of **antibiotic exposure** decreased in the experimental group (RR: 0.55, 95% CI: 0.51–0.60; P = 0.003). In the per-protocol analysis, the median **duration of antibiotic** therapy was 2 days shorter in the PCT group (5 days, range 3–6) than in the control group (7 days, range 5–9, P < 0.001). All patients survived to follow up at 4 weeks, and laboratory and **clinical outcome measures** were similar for the two groups.

The last three studies that referred to community-acquired pneumonia were not exclusively focused on pneumonia but analyzed the use of biomarkers in respiratory tract infections including CAP:

The study by Philipp Schuetz *et al.* [17] was a multicenter, non-inferiority, randomized controlled trial which included 1381 patients with a primary diagnosis of LRTI at ED. In the PCT group (n = 687), the administration of antibiotics was based on a PCT algorithm, while in standard group (n = 694) administration of antibiotics was given

according to standard guidelines. A total of 103 patients in the PCT group (15.4%) vs 130 patients (18.9%) in the control group reached the primary endpoint of **combined adverse outcome within 30 days of emergency department (ED) admission** (death from any cause, intensive care unit (ICU) admission for any reason, disease-specific complications, and recurrence of lower respiratory tract infection (LRTI) in need of antibiotics with or without hospital readmission). The 95% CI for the risk difference (−7.6% to 0.4%) excludes an excess risk in the PCT group of 7.5% or more satisfying the predefined noninferiority criterion and the same holds true for the analysis on the per-protocol population. Prescription rates and overall antibiotic exposure were significantly reduced in the PCT group for the whole population as well as in all LRTI subgroups.

Christ-Crain *et al.* [18] conducted a prospective, cluster-randomized (with workwise cluster-randomization), controlled, single-blinded intervention trial, including 243 eligible patients with suspected LRTI who allocated in PCT group (n=124) where antibiotic discontinuation was considered according to PCT values and PCT algorithm, and the standard group (n=119) where antibiotic treatment was based on standard of care. The proportion of patients with lower respiratory tract infections who received antibiotics was reduced by 47% compared to the standard group (p<0·0001). In the subgroup of patients with acute exacerbations of COPD the reduction was 56% (p=0·0001). The relative risk of antibiotic exposure in the procalcitonin group was 0·49 (0·44–0·55, p<0·0001). No significant differences were found at secondary outcomes.

Finally, Matthias Briel *et al.* [10] conducted a randomized, open, multicenter, noninferiority trial. 458 patients were assigned to the PCT group (n = 232) where the PCT measurements determined the prescription and the duration of antibiotic therapy, or standard group (n = 226), where antibiotic therapy was decided according to physician. Of the 455 patients interviewed at 14 days (per protocol analysis), both groups had a mean of 8.7 **days with restricted daily activities**. An adjusted increase of 0.1 days with restricted activities (95% CI, −0.5 to 0.8 days) while receiving PCT-guided therapy met the criterion for noninferiority. Physicians **prescribed antibiotics** for 58 of the 232 patients (25%) with PCT-guided therapy and for 219 of 226 patients (97%) with standard therapy (percentage decrease while receiving PCT-guided therapy, 72% [95% CI, 66%–78%]; adjusted odds ratio, 0.01 [95% CI, 0.002–0.018]). The mean **duration of antibiotic treatment** in patients receiving antibiotics was 6.2 days in the PCT group and 7.1 days in the control group (adjusted decrease with PCT, 1.0 days [95% CI, 0.4–1.7 days]).

VAP (VENTILATOR-ACQUIRED PNEUMONIA)

Three studies that met the inclusion criteria, investigated the utility of biomarkers in the management of ventilation-associated pneumonia. From these studies, two used procalcitonin as reference biomarker for the interventions and one study used IL-1β and IL-8 measured in broncho alveolar lavage (BAL).

Mazlan M. *et al.* [19] conducted a single-blinded randomized control trial. The PCT group (n=43) used point-of-care PCT measurements and standard monitoring to determine the duration of antibiotic therapy. The control group (n=42) used only standard monitoring. The mean **antibiotic treatment duration** was significantly lower by 1.25 days in the PCT group than in the control group (10.28 [2.68] days vs. 11.52 [3.06]), with a 95% CI of −2.48 to −0.01, p= 0.049). The PCT group also had a higher **number of antibiotic-free days alive** during the 28 days after VAP onset than the control group (10.79 [7.61] days vs. 8.72 [6.41] days), although the difference was not statistically significant. No significant associations between organism type, antibiotic use, retreatment, and **mortality** were found in the two-group comparison.

The trial by Stolz *et al.* [21] was a multinational, randomized controlled open intervention one in patients with VAP admitted in the ICU. In the PCT group (n = 51), antibiotic treatment discontinuation was decided according to PCT measurements, whereas in the control group (n = 50) antibiotic treatment was considered according to current guidelines. The median (IQR) **number of antibiotic-free days alive within 28 days of diagnosis of VAP** was significantly higher in the procalcitonin group than in the control group (13 (2–21) versus 9.5 (1.5–17) days). The researchers found no statistical significance in the secondary outcomes or **physiological changes** between the two groups during the 28-day follow-up.

Hellyer *et al.* [7] conducted a multi-center, randomized controlled trial in patients admitted to 24 ICUs from 17 National Health Service hospital, including 214 intubated patients with suspected VAP (≥18 years old, mechanical ventilation for ≥48h). These patients were randomly assigned to

biomarker-guided (IL-1β and IL-8) recommendation on antibiotics (intervention group, n = 104) or routine use of antibiotics (control group, n = 106). No significant difference in the primary outcome (**antibiotic-free days** in the 7 days following bronchoalveolar lavage) or the secondary outcomes was found. Interestingly, median antibiotic days at day 7 were 6 (IQR 4–7) in both groups (hazard ratio [HR] 0·84, 95% CI 0·63–1·12), and no differences in antibiotic-free days (at 14 days or 28 days) were reported.

ASPIRATION PNEUMONIA

The publication from Ogasawara T. *et al.* [22] was based on a prospective, randomized, open-label, non-inferiority trial. The duration of antibiotic therapy was based on PCT levels upon admission (n=48) or according to the standard guideline (n=48). The intervention did not lead to an increase in the primary outcome **of relapse of aspiration pneumonia and death** from any cause within 30 days., while the **median duration for antibiotic exposure** was significantly lower in the PCT group (5 versus 8 days; p=0.0001).

HAP (HOSPITAL ACQUIRED PNEUMONIA)

Gavazzi 2022 PROPAGE (PROcalcitonine chez les Patients AGEs) [23] was an interventional, randomized, comparative, open-label study involving 117 elderly patients admitted for pneumonia to eight geriatric units with HAP. These patients were randomized into PCT group (n = 56) who were treated according to two PCT algorithms for determining the duration of antibiotic therapy and control group (n = 60). Median **duration of antibiotic therapy** in the PCT group was 8 days (IQR: 6–11 days), which was significantly shorter than in the control group (10 days, IQR: 8–12, p = 0.001). The **recovery rate** on day 45 in the PCT group (84%) was lower than that measured on the control group (89.5%), but no statistically significant difference was observed in recovery rate between the two groups (p = 0.402).

EXACERBATION OF COPD (ECOPD)

Daubin C. *et al.* [24] conducted a randomized controlled trial that investigated the PCT-guided antibiotic treatment on patients with severe acute exacerbation of COPD. In the PCT group (n = 151), the antibiotic treatment was guided by serum procalcitonin levels and in the control group (n = 151) antibiotic therapy was guided by standard of care. The primary outcome was the **3-months mortality**: [30 (20%) in the PCT group and 21 (14%) in the control group; adjusted difference, 6.6%; 90% CI −0.3 to 13.5%]. The number of patients in the PCT group who received antibiotics was significantly lower than the number of patients in the control group.

The study by Stolz D. *et al.* [9] is a single-center, randomized, controlled trial that included patients requiring hospitalization for ECOPD. The initiation and discontinuation of antibiotic therapy was determined either from the PCT levels in the PCT group (n = 113) or by the usual care in the standard group (n = 113). The experimental strategy significantly reduced **antibiotic prescriptions** (40% vs 72%, p <0.0001) **and antibiotic exposure** (RR, 0.56; 95% CI, 0.43 to 0.73; p < 0.0001), compared to standard therapy. During the follow up the clinical and laboratory outcome measures did not show significant differences between the two groups. Procalcitonin-guided therapy and standard therapy were equivalent in terms of clinical success rate (82.4% vs 83.9%, p= 0.853).

Christofer Butler *et al.* [8] study was a multicenter, parallel arm, randomized controlled trial including 653 patients with an acute ECOPD. Patients randomized into the **CRP guided antibiotic treatment group** (n = 325) or usual care group (n = 324). Antibiotics were prescribed for ECOPD by 212 out of 274 participants (77.4%) and 150 out of 263 participants (57.0%) in the usual-care and CRP POCT arm, respectively [adjusted odds ratio 0.31, 95% confidence interval (CI) 0.20 to 0.47].

QUALITY ASSESSMENT, RISK OF BIAS (ROB)

None of the studies had low risk of bias in all seven Cochrane RoB 1 domains (Fig. 2). We found that 81% of the studies had high risk of bias due to outcome assessors not being masked (detection bias) and 56% to be at high risk of performance bias as participants and personnel were not masked. 31% of the studies had low risk of selection bias due to allocation concealment and in 62% the risk of bias was unclear. 1 study had high risk of selection bias due to randomization (M. Christ Crain 2004) [18]. 3 (19%) studies were judged with high risk of attrition bias and incomplete outcome data (Gavazzi, lhopitallier, Hellyer) [23, 11, 7]. Selective reporting bias was low risk in 75% of the studies. The randomized clinical trial by Wussler D. 2019 [14] had high risk of detection bias, high risk of selective reporting bias and unclear the other domains (Fig. 3).

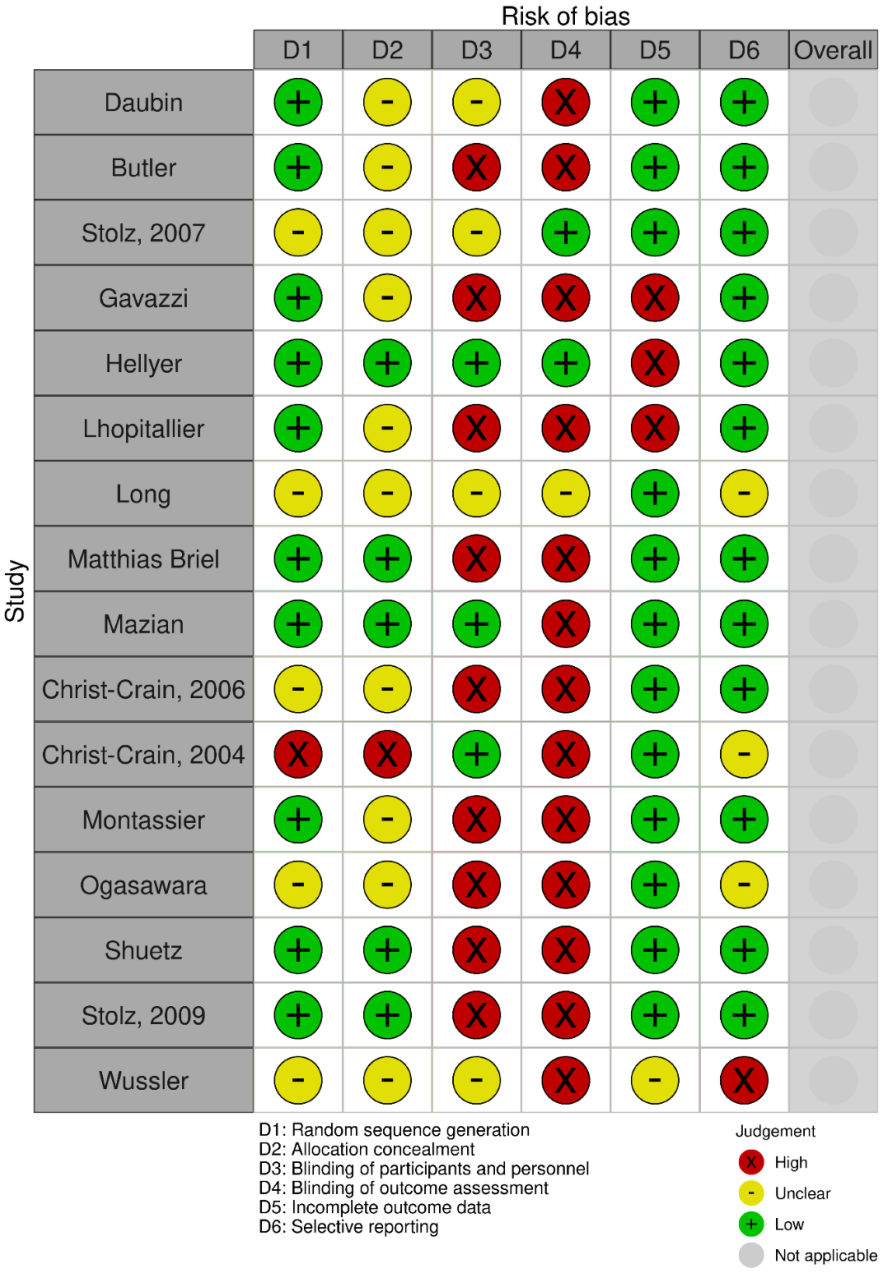


Figure 2. Quality assessment according to Cochrane RoB 1 domains.

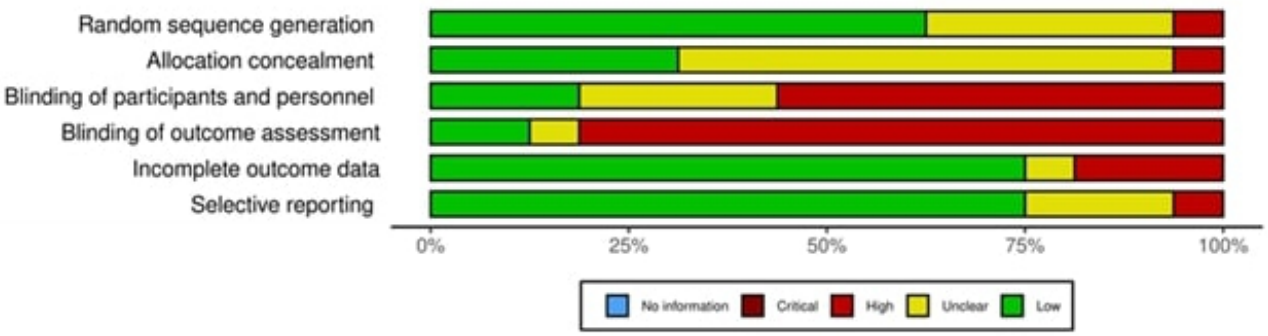
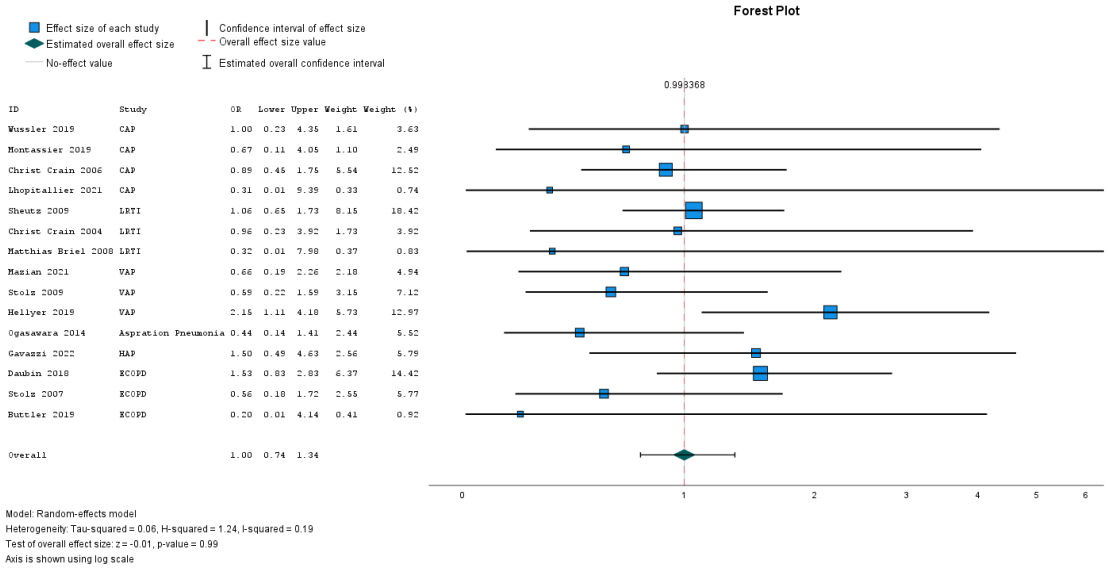


Figure 3. Aggregated qualitative assessment for each Cochrane RoB 1 domain.

OUTCOME SYNTHESIS

MORTALITY

Mortality was reported by a total of 15 studies, 4 of which were on CAP [8,10, 12,13], 3 on LRTIs [11,17,18], 3 on VAP [7,19,21], 1 on aspiration pneumonia [22], 1 on HAP [23] and 3 on COPD exacerbation [8,9,24]. Most of the studies had wide confidence intervals. In a total of 4751 patients (2396 in the intervention and 2355 in the control group), the biomarker-based approach did not lead to increased mortality [summary OR was 0.998 (95%CI: 0.74–1.34, p value: 0.991). I2:19%].



ANTIBIOTIC USE

Antibiotic Prescription: 9 studies reported this outcome, four of the studies included patients with CAP [11,12, 13,16], three included patients with LRTI [17,18,10] and two included patients with COPD [9,10]. This outcome was measured at different time-points ranging from antibiotic prescription on admission-initial consultation up to 30-day follow-up. All the studies found a significant reduction of antibiotic prescription when PCT-based practice was employed. One study reported positive results on the use of CRP [8]. Lhopitallier *et al.* reported this outcome at three different time-points (0, 7 and 28 days) and Buttler *et al.* at 0 days and 4 weeks after (Fig. 4).

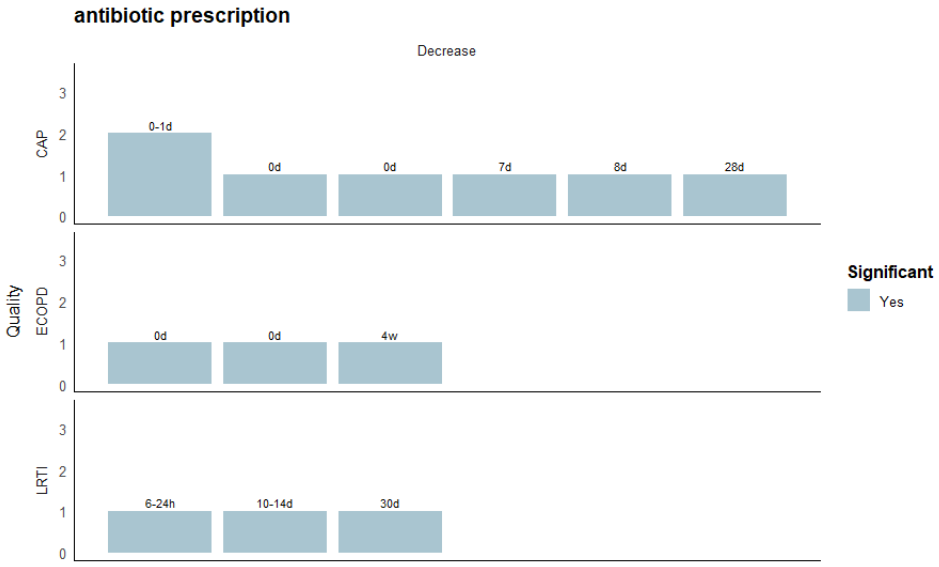


Figure 4. Harvest plot of studies on Antibiotic Prescription.

Duration of Antibiotic Therapy: 4 studies on CAP with conflicting results on the effect of PCT-based practice on the duration of antibiotic therapy were found [12,13,14,16]. Contrariwise, all studies on VAP (2) [19,21], LRTIs (3) [17,18,10], aspiration pneumonia (1) [22], HAP (1) [23] and COPD exacerbation (1) [24] favored intervention (Fig. 5).

Number of antibiotic-free days alive: Neither Mazlan nor Stolz [19,21] found important significance regarding this outcome.

Rate of antibiotic exposure: All 5 studies (4 on PCT [13,18,17,9] and 1 on CRP [8]) concluded that the biomarker-based practice significantly reduced the rate of antibiotic exposure. Stolz *et al.* reported data on 14–21 days and 6 months later (Fig. 6).

Other outcomes: Two studies reported on the use of antibiotics as "antibiotic persistence rate" [23] and "antibiotic discontinuation rate" [21], with both favoring the biomarker-based intervention. Additionally, 5 studies reported significant reduction of the rate of antibiotic exposure at the short and long term- follow-up.

The study by Hellyer [7] that investigated interleukins measured in BAL of patients with VAP did not report significant difference regarding the number of antibiotic-free days alive and the duration of antibiotic therapy.

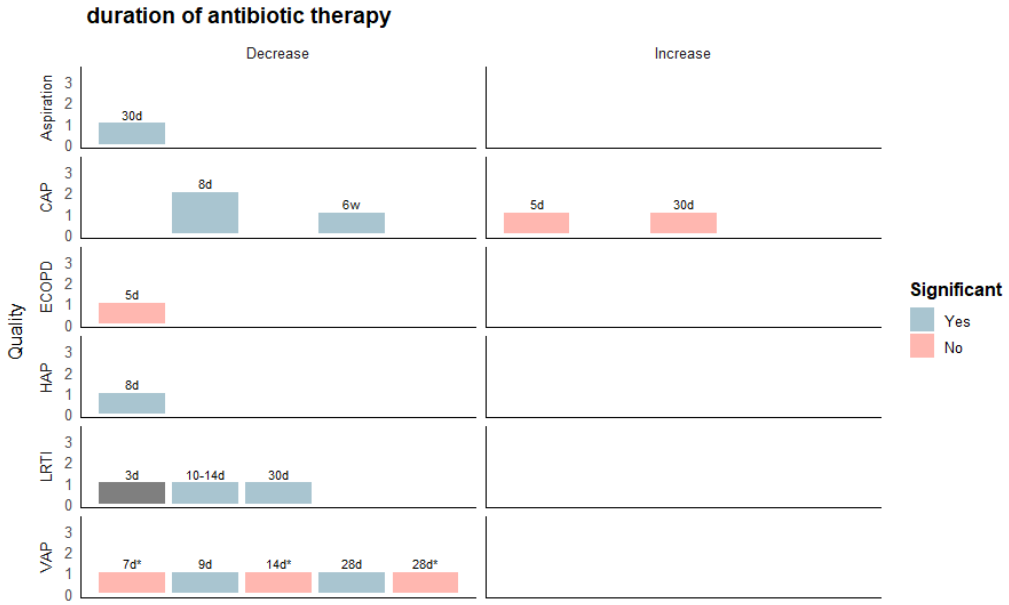


Figure 5. Harvest plot of studies on Duration of antibiotic therapy.

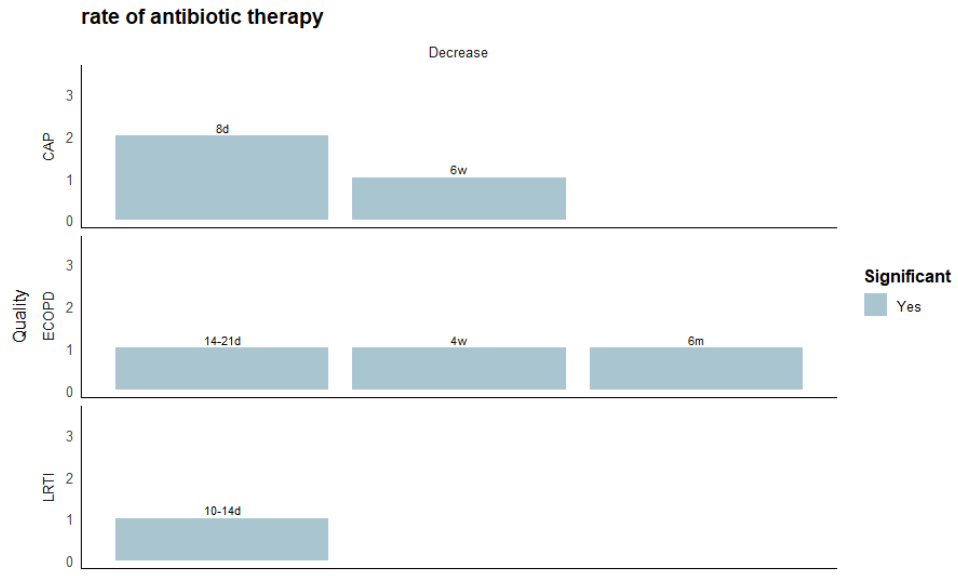


Figure 6. Harvest plot of studies on rate of antibiotic exposure.

ANTIBIOTIC ADVERSE EFFECTS

Only 5 studies [17,22,8,7,11] included data on the effect of biomarker-based practice for the reduction of antibiotic related adverse effects, such as antibiotic-associated infections. The studies by Scheutz and Lhopitallier reached statistical significance regarding that parametr. It should be noted that the study by Scheutz a total of 1381 patients were enrolled. A total of 331 adverse events were recorded, while other studies had a much smaller number of enrollees and events (Fig. 7).

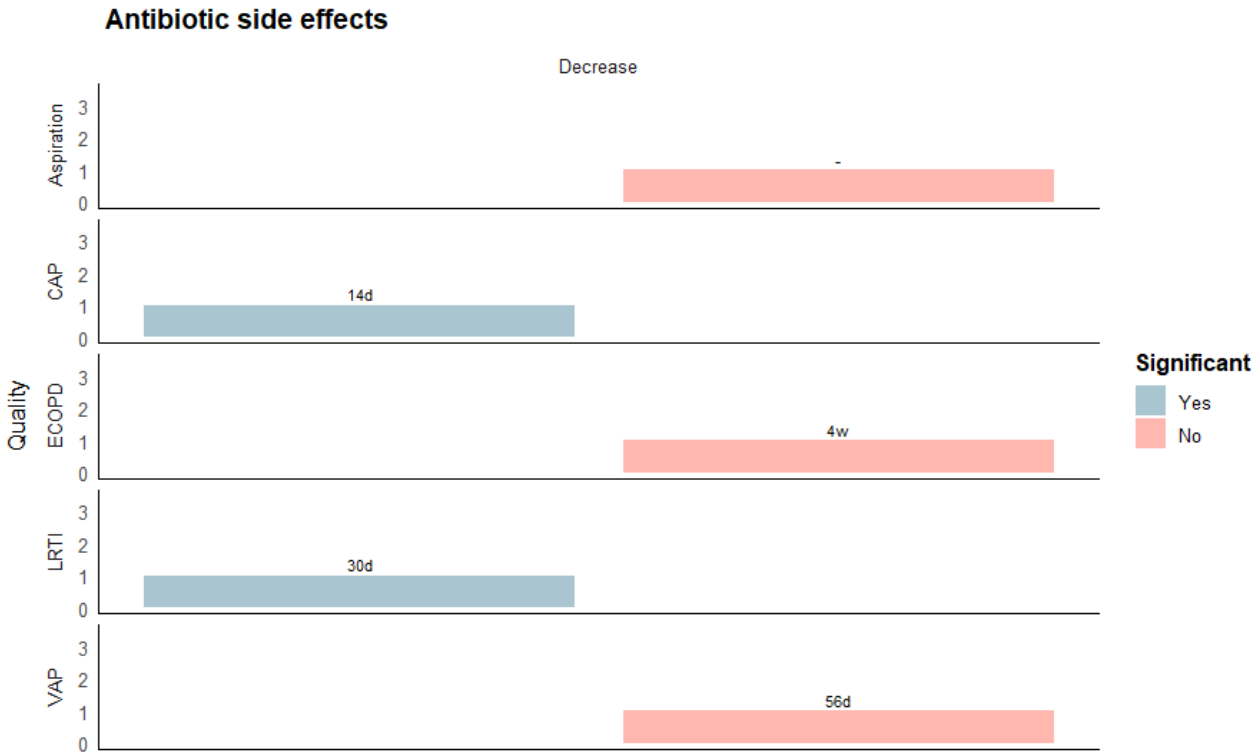


Figure 7. Harvest plot of studies on rate of antibiotic-related adverse effects.

RECURRENCE/ RETREATMENT

9 studies [10,12,13,17,18,19,21,22,23] followed patients for up to 6 months, with most of them focusing on the first 30 days after enrollment to PCT-based practice. This outcome was assessed in different ways such as need for hospitalization, radiologic recurrence, symptoms re-exacerbation, etc. Only the study of Sheutz *et al.* found a significant difference between the two groups (favoring control) (Fig. 8).

ICU ADMISSION

The need for ICU admission was considered in 4 studies, all of which investigated the use of PCT [9,13,17,18]. None of the included studies suggested either a positive or a deleterious effect from the use of PCT-based practice in this outcome.

MECHANICAL VENTILATION FREE DAYS

Stolz [21] reported that there was no significant difference between the intervention and control groups.

LENGTH OF HOSPITALIZATION

This outcome was reported by 9 studies in total [7,9,12,13,14,17,18,21,22]. The median length of hospitalization was similar between the intervention and the control group in all studies. In the studies that investigated patients with VAP and aspiration pneumonia the median length of hospitalization ranged from 26 to 30 day, while it was substantially lower in other types of pneumonia.

RATE OF HOSPITALIZATION

7 studies [8,9,10,11,12,13,18] report this outcome on different time-points ranging from need for immediate hospitalization (at ED or within 24hours) to up to 6 months after first evaluation (Fig. 9).

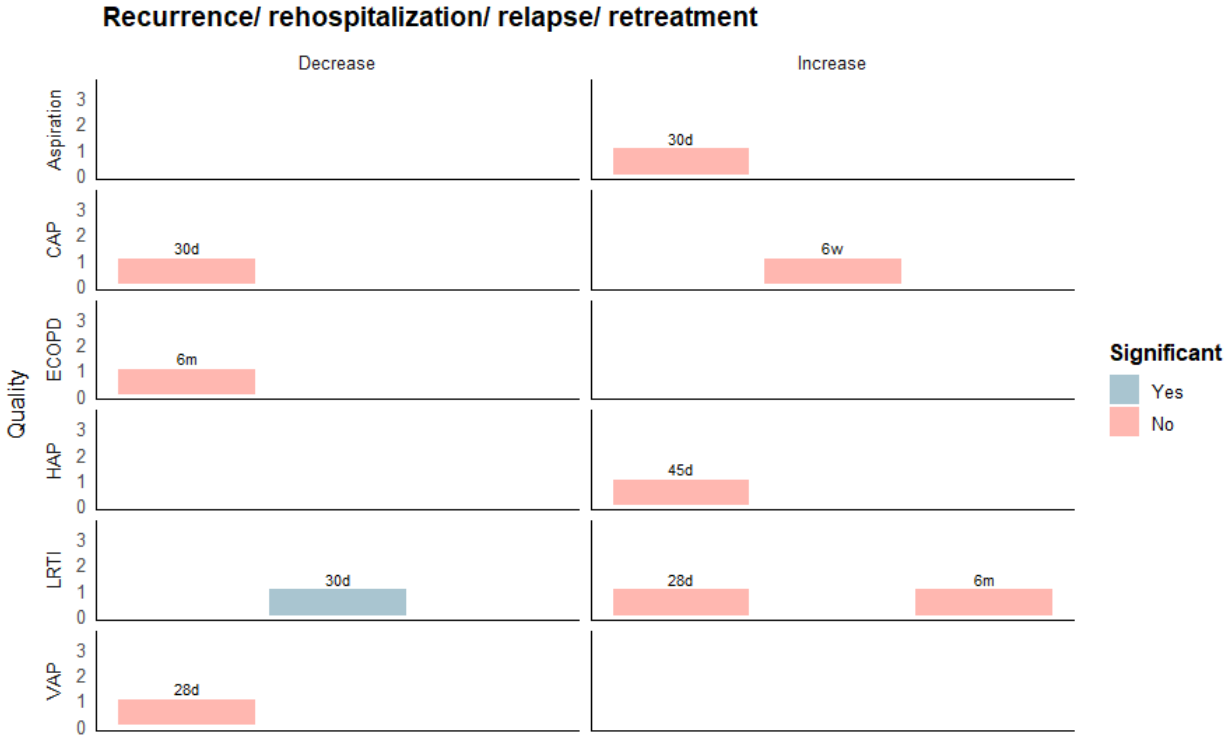


Figure 8. Harvest plot of studies on recurrence – rehospitalization – relapse – retreatment.

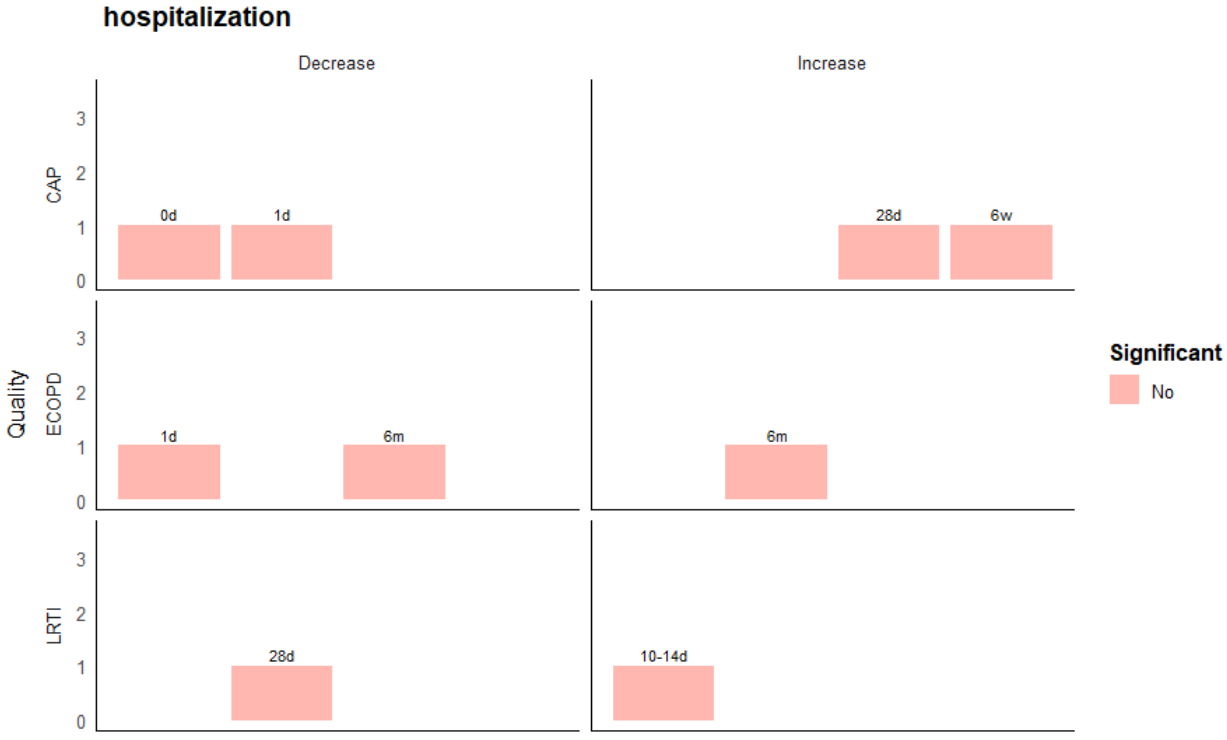


Figure 9. Harvest plot of studies on rate of hospitalization.

CLINICAL CURE RATE/FAILURE

Out of the 7 trials dealing with that that outcome [7,8,11,12,13,16,23], only one study by Buttler *et al.* [8] found a significant difference between the biomarker-based intervention and the control groups. Specifically, the total score of the Clinical COPD Questionnaire at 2 weeks favored the CRP-guided group. Hellyer *et al.* studies this outcome in patients with VAP in 3 different timepoints (3, 7 and 14 days) (Fig. 10).

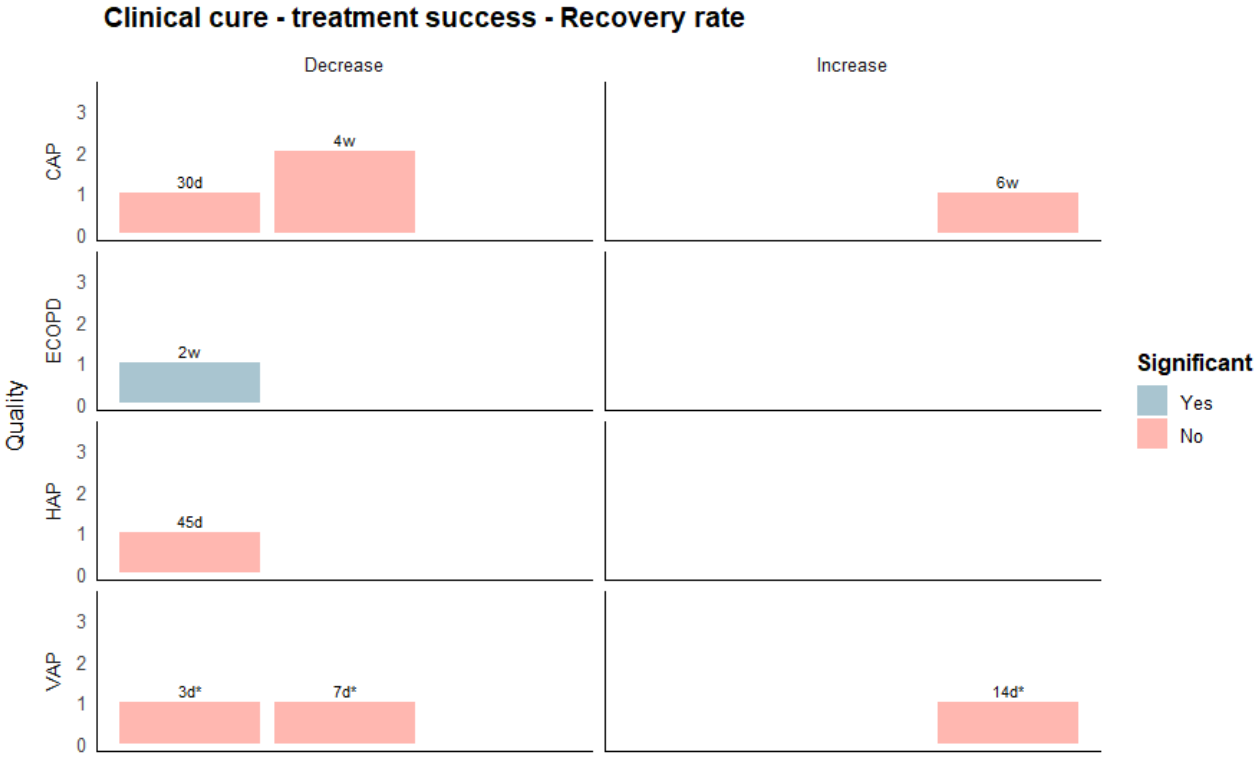


Figure 10. Harvest plot of studies on clinical cure-treatment success- recovery rate.

DURATION OF SYMPTOMS

Only the study by Lhopitallier [11] reported this outcome. There was on difference between the three arms of the trial (PCT, ultrasound+PCT, control) regarding the duration of symptoms.

DURATION OF RESTRICTED ACTIVITIES

The duration of restricted activities by day 14 was similar between the intervention and the control groups in both the Lhopitallier and the Mathias Briel trials [11,10].

ADVERSE EVENTS

Only the study by Hellyer [7] reported serious adverse events after the intervention procedure (BAL bronchoscopy). This outcome refers to events, such us, VF arrest, death, tension pneumothorax, endotracheal tube displacement, cardiac arrest, etc. within 2 hours of bronchoscopy. No significant difference was observed between the intervention and control group.

DISCUSSION

In this review we systematically searched the literature for clinical trials investigating the use of biomarkers of inflammation in guiding clinical practice in patients with pneumonia. A total of 16 studies were included, the majority of which investigated serum procalcitonin. Additionally, we found one study on serum PCR and one study on interleukins (IL1-b, IL-8) measured in BAL. Different types of pneumonia and settings were considered by the included trials, ranging from low-risk CAP in outpatients to VAP in ventilated patients in the ICU.

Taking into consideration the clinical heterogeneity expected by the wide inclusion criteria that we used, we refrained from performing quantitative synthesis and meta-analysis in the

majority of the included outcomes. Nevertheless, clear themes emerged from the qualitative synthesis. Biomarker guided clinical practice led to a positive effect in most of the antibiotic-related outcomes, such as the rate of antibiotic prescription, antibiotic duration, and antibiotic exposure. At the same time, biomarker-based practice did not seem to lead to more adverse clinical outcomes, such as higher mortality, treatment failure or need for hospitalization. The effect of biomarker-based practice on the reduction of antibiotic-related adverse effects should be further investigated, as lower antibiotic exposure might decrease adverse effects (e.g. C. Difficile infections) as well. However, the confidence in these findings is limited by the high risk of bias that was introduced in most of the included studies, mainly deriving from lack of outcome assessors' blinding.

The search for the ideal biomarker for pneumonia is ongoing. Among all the potential biomarkers, C-reactive protein and procalcitonin are the most extensively studied and used in clinical practice, and their role in triage, diagnosis, risk stratification, monitoring clinical course, and antibiotic stewardship has been extensively assessed. Biomarkers can be employed in different manners to assist. Moreover, the dynamic monitoring of changes in biomarker levels can be a useful helpful tool for the prompt selection of individual therapies [25]. The significance of antibiotic stewardship and the urgent need to reduce unnecessary antibiotic prescription has been highlighted by many researchers and scientific societies. Nevertheless, it is often overlooked by clinicians, and this can be partly attributed to the lack of standardized tools to guide antibiotic use. The results of our review suggest that biomarker-based practice can lead to significant reduction in antibiotic prescription using simple point of care adjunct tools.

From clinical experience and the current trends in the literature, it is apparent that one inflammatory biomarker cannot fill every clinical gap, and thus research should focus on the strengths of each biomarker. For example, Procalcitonin seems to be unable to distinguish viral from bacterial pneumonias, but an elevated PCT is a significant risk factor for mortality in CAP [26,27]. Similar to our findings, an IPD meta-analysis of patients with infection/sepsis in ICU showed that PCT based practice can lead to lower antibiotic treatment duration [15].

Procalcitonin has been put in the spotlight current literature. An updated Cochrane Review suggested that its use in clinical practice can lead to lower risks of mortality, antibiotic consumption and antibiotic related effects [28]. These high-quality results should open the road for research in additional settings and biomarkers. However, as evidenced by our review, there is still a lack of published trials studying other biomarkers in this field. It should be noted that this Cochrane Review, included patients with upper respiratory tract infections, such as sinusitis, tonsilitis and otitis media. Another recently published Cochrane Review that assessed point-of care biomarkers for antibiotic prescription in patients with acute respiratory tract infections included 12 pediatric trials on CRP and 1 adult trial on PCT. The found high-certainty evidence that CRP-guided approach significantly reduces antibiotic prescription, without negatively affecting mortality and recovery rates [29]. Most importantly, they concluded that it is unlike that further studies would change these results. In line with our findings, the researchers note that additional research in vulnerable populations (e.g. elderly and immunocompromised) and in newer biomarkers is justified.

The lack of conformity in the algorithms of PCT-guided decision making poses an additional hurdle, when translating clinical trial results to real-world practice. In 2019, a consensus-based approach by field experts suggested three different algorithms based on severity and setting (ICU and non-ICU) [30]. In this article, the importance of education of all stakeholders is highlighted as an important key step for integrating these algorithms in clinical practice.

Finally, health systems should also consider the cost-effectiveness of these biomarker-based practices. An economic-evaluation of PCT-guided antibiotic therapy showed that it could lead to substantial savings both in the inpatient and outpatient settings [31]. A systematic review that included patients presenting in the ED with suspected bacterial infection (almost exclusively studies with patients with respiratory symptoms) showed that PCT-guided treatment has a probability of ≥84% of being cost-effective for all settings and populations considered [32].

Although, dozens of biomarkers have emerged in the last decades we only found published randomized studies for PCT, CRP and interleukins [20]. This should raise concerns regarding the quality and the scope of the research in this field. Validation of novel biomarkers is of utmost importance and thus, we should focus on proving the clinical benefit that can be gained from

biomarker-guided clinical practice. Additionally, the combination of using inflammatory biomarkers in the management of sepsis patients, also the role of severity scores accompanied to biomarkers needs further assessment. The scientific community should explore different clinical scenarios referring to patient groups and settings, while taking advantage of the plethora of observational studies currently existing in the literature.

The main limitation of this review is the lack of quantitative synthesis in outcomes other than mortality and consequently no recommendations for clinical practice can be made. This choice was made due to the nature and the heterogeneity of our results, which should be considered as a deviation from our published protocol. However, we attempted to present data on significant outcomes both for patients and clinicians, in such a way that can inspire the conduction of quality research in the future. Additionally, our searches were limited to one major database, which lead to lower sensitivity in our search strategy. Our review protocol was registered in PROSPERO after the piloting of the searches and the study selection process had been completed, but before the formal commencement of the full review process.

CONCLUSION

Biomarker-guided clinical practice may improve provided healthcare, in terms of reduced antibiotic consumption with no inferiority to mortality, relapses and exacerbations in patients with different types of pneumonia. Thus, such approaches should be further evaluated in order to achieve personalized medicine. Further research should focus in minimizing risk of bias and assessing novel biomarkers in specific settings and vulnerable populations.

Obiective: Practica clinică bazată pe biomarkeri câștigă în prezent teren și este implicată din ce în ce mai mult luarea deciziilor. O varietate de biomarkeri au fost studiați de-a lungul anilor și unii dintre ei au deja un rol stabilit în medicina modernă, cum ar fi procalcitonina (PCT), care a fost propusă pentru a reduce expunerea la antibiotice. Ne-am propus să revizuim sistematic toți biomarkerii examinați pentru a ghida practica clinică la pacienții cu pneumonie.

Metode: O revizuire sistematică a PubMed a fost efectuată în aprilie 2023 de către doi cercetători independenți folosind ghidurile PRISMA. Au fost incluse studiile randomizate care au înrolat pacienți cu pneumonie și au comparat strategiile ghidate de biomarkeri cu standardele de îngrijire.

Rezultate: Au fost înregistrate 1242 de studii, dintre care 16 au fost eligibile pentru acest studiu. 14 studii au investigat PCT ca biomarker. Dintre acestea, 8 studii au raportat asupra pneumoniei dobândite în comunitate (PAC), 2 asupra pneumoniei asociate ventilatorului (VAP), 1 asupra pneumoniei prin aspirație, 1 asupra pneumoniei dobândite în spital (HAP) și 2 asupra exacerbarii bolii pulmonare obstructive cronice (EPOC). A existat 1 studiu, referit la VAP, care a investigat interleukina-1β (IL-1β) și interleukina-8 (IL-8) și 1 studiu care a raportat rolul proteinei C-reactive (CRP) în ECOPD. Într-un total de 4751 de pacienți din 15 studii, abordarea bazată pe biomarkeri nu a condus la creșterea mortalității [OR: 0,998 (95%CI: 0,74-1,34, valoarea p: 0,991). I2:19%]. Printre diferitele tipuri de pneumonie, practica ghidată de biomarkeri pare să îmbunătățească rezultatele legate de antibiotice, cum ar fi rata prescrierii antibioticelor, durata terapiei cu antibiotice și rata expunerii la antibiotice, în timp ce 5 studii au raportat o posibilă scădere a antibioticelor. -efecte adverse asociate. Practica ghidată de biomarkeri nu pare să ducă la o creștere a altor efecte adverse, cum ar fi nevoia de spitalizare și durata spitalizării. Cu toate acestea, studiile incluse au un risc ridicat de eroare sistematică, în principal din cauza orbirii necorespunzătoare a participanților/personalului și a evaluatorilor de rezultate.

Concluzie: Practica clinică ghidată de biomarkeri îmbunătățește asistența medicală oferită, în ceea ce privește consumul redus de antibiotice nu a dus la o creștere față de mortalitate, recăderi și exacerbări la pacienții cu diferite tipuri de pneumonie. Așadar, astfel de abordări ar trebui evaluate în continuare pentru a realiza o medicină personalizată.

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SUPPLEMENTARY TABLE 1 – SEARCH STRATEGY

Search number	Query	Sort By	Filters	Search Details	Results
47	#45 NOT #46	Most Recent		(("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields] OR ("bronchopneumonia"[MeSH Terms] OR "bronchopneumonia"[All Fields] OR "bronchopneumonias"[All Fields] OR "bronchopneumoniae"[All Fields]) OR "CAP"[All Fields] OR "HAP"[All Fields] OR "VAP"[All Fields] OR ("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR ("acute"[All Fields] AND "respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "acute respiratory distress syndrome"[All Fields]) OR ("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR "ards"[All Fields])) AND ("procalcitonin"[MeSH Terms] OR "procalcitonin"[All Fields] OR "procalcitonine"[All Fields] OR "SUPAR"[All Fields] OR (("solubility"[MeSH Terms] OR "solubility"[All Fields] OR "solubilities"[All Fields] OR "soluble"[All Fields] OR "solubles"[All Fields] OR "solublization"[All Fields] OR "solublize"[All Fields] OR "solublized"[All Fields]) AND ("receptors, urokinase plasminogen activator"[MeSH Terms] OR ("receptors"[All Fields] AND "urokinase"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "urokinase plasminogen activator receptors"[All Fields] OR ("urokinase"[All Fields] AND "receptor"[All Fields]) OR "urokinase receptor"[All Fields])) OR ("interleukine"[All Fields] OR "interleukines"[All Fields] OR "interleukins"[MeSH Terms] OR "interleukins"[All Fields] OR "interleukin"[All Fields]) OR ("curr res psychol"[Journal] OR "crp"[All Fields]) OR ("c reactive protein"[MeSH Terms] OR ("c reactive"[All Fields] AND "protein"[All Fields]) OR "c reactive protein"[All Fields] OR "c reactive protein"[All Fields]) OR (("inter alpha inhibitor"[Supplementary Concept] OR "inter alpha inhibitor"[All Fields] OR "inter alpha inhibitor"[All Fields]) AND ("protein s"[All Fields] OR "proteinous"[All Fields] OR "proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])) OR ("phospholipases"[MeSH Terms] OR "phospholipases"[All Fields] OR "phospholipase"[All Fields] OR "phospholipasic"[All Fields]) OR ("bactericidal permeability increasing protein"[Supplementary Concept] OR "bactericidal permeability increasing protein"[All Fields]) OR "CD64"[All Fields] OR ("selenoproteins"[MeSH Terms] OR "selenoproteins"[All Fields] OR "selenoprotein"[All Fields]) OR ("lipopolysaccharide binding protein"[Supplementary Concept] OR "lipopolysaccharide binding protein"[All Fields] OR "lipopolysaccharide binding protein"[All Fields]) OR ("syndecans"[MeSH Terms] OR "syndecans"[All Fields] OR "syndecan"[All Fields]) OR ("plasminogen inactivators"[MeSH Terms] OR ("plasminogen"[All Fields] AND "inactivators"[All Fields]) OR "plasminogen inactivators"[All Fields] OR ("plasminogen"[All Fields] AND "activator"[All Fields] AND "inhibitor"[All Fields]) OR "plasminogen activator inhibitor"[All Fields]) OR (("plasminogen activators"[MeSH Terms] OR ("plasminogen"[All Fields] AND "activators"[All Fields]) OR "plasminogen activators"[All Fields] OR ("plasminogen"[All Fields] AND "activator"[All Fields]) OR "plasminogen activator"[All Fields]) AND "inhibito"[All Fields]) OR ("thrombomodulin"[MeSH Terms] OR "thrombomodulin"[All Fields] OR "thrombomoduline"[All Fields] OR "thrombomodulins"[All Fields]) OR ("fibrinogen"[MeSH Terms] OR "fibrinogen"[All Fields] OR "fibrinogens"[All Fields] OR "fibrinogen s"[All Fields] OR "fibrinogene"[All Fields]) OR ("angiopoietins"[MeSH Terms] OR "angiopoietins"[All Fields] OR "angiopoietin"[All Fields]) OR ("adrenomedullin"[MeSH Terms] OR "adrenomedullin"[All Fields] OR "adrenomedullins"[All Fields]) OR ("azu1 protein human"[Supplementary Concept] OR "azu1 protein human"[All Fields] OR "heparin binding protein"[All Fields]) OR ("fibrin fragment d"[Supplementary Concept] OR "fibrin fragment d"[All Fields] OR "d dimer"[All Fields]) OR ("chitinase 3 like protein 1"[MeSH Terms] OR "chitinase 3 like protein 1"[All Fields] OR "ykl 40"[All Fields]) OR ("copeptin"[All Fields] OR "copeptine"[All Fields]) OR ("intercellular adhesion molecule 1"[MeSH Terms] OR ("intercellular"[All Fields] AND "adhesion"[All Fields] AND "molecule 1"[All Fields]) OR "intercellular adhesion molecule 1"[All Fields] OR "icam 1"[All Fields]) OR ("lithostathine"[MeSH Terms] OR "lithostathine"[All Fields] OR ("pancreatic"[All Fields] AND "stone"[All Fields] AND "protein"[All Fields]) OR "pancreatic stone protein"[All Fields]) OR ("neopterin"[MeSH Terms] OR "neopterin"[All Fields] OR "neopterine"[All Fields]	1,242

			OR "neopterins"[All Fields]) OR ("macrophage migration inhibitory factors"[MeSH Terms] OR ("macrophage"[All Fields] AND "migration inhibitory"[All Fields] AND "factors"[All Fields]) OR "macrophage migration inhibitory factors"[All Fields] OR ("macrophage"[All Fields] AND "migration"[All Fields] AND "inhibitory"[All Fields] AND "factor"[All Fields]) OR "macrophage migration inhibitory factor"[All Fields]) OR ("High-mobility"[All Fields] AND "group-box"[All Fields] AND "1"[All Fields] AND ("protein s"[All Fields] OR "proteinous"[All Fields] OR "proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])) OR "Endocan"[All Fields] OR ("pentraxin"[All Fields] OR "pentraxins"[All Fields]) OR ("hepcidin s"[All Fields] OR "hepcidine"[All Fields] OR "hepcidins"[MeSH Terms] OR "hepcidins"[All Fields] OR "hepcidin"[All Fields]) OR ("calprotectine"[All Fields] OR "leukocyte l1 antigen complex"[MeSH Terms] OR ("leukocyte"[All Fields] AND "l1"[All Fields] AND "antigen"[All Fields] AND "complex"[All Fields]) OR "leukocyte l1 antigen complex"[All Fields] OR "calprotectin"[All Fields])) AND ("randomiz*"[All Fields] OR ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]))) NOT ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]) OR "SARS-COV2"[All Fields])
46	COVID-19 OR SARS-COV2	Most Recent	"covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]) OR "SARS-COV2"[All Fields]	352,239
45	#43 AND #44	Most Recent	("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields] OR ("bronchopneumonia"[MeSH Terms] OR "bronchopneumonia"[All Fields] OR "bronchopneumonias"[All Fields] OR "bronchopneumoniae"[All Fields]) OR "CAP"[All Fields] OR "HAP"[All Fields] OR "VAP"[All Fields] OR ("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR ("acute"[All Fields] AND "respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "acute respiratory distress syndrome"[All Fields]) OR ("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR "ards"[All Fields])) AND ("procalcitonin"[MeSH Terms] OR "procalcitonin"[All Fields] OR "procalcitonine"[All Fields] OR "SUPAR"[All Fields] OR (("solubility"[MeSH Terms] OR "solubility"[All Fields] OR "solubilities"[All Fields] OR "soluble"[All Fields] OR "solubles"[All Fields] OR "solublization"[All Fields] OR "solublize"[All Fields] OR "solublized"[All Fields]) AND ("receptors, urokinase plasminogen activator"[MeSH Terms] OR ("receptors"[All Fields] AND "urokinase"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "urokinase plasminogen activator receptors"[All Fields] OR ("urokinase"[All Fields] AND "receptor"[All Fields]) OR "urokinase receptor"[All Fields])) OR ("interleukine"[All Fields] OR "interleukines"[All Fields] OR "interleukins"[MeSH Terms] OR "interleukins"[All Fields] OR "interleukin"[All Fields]) OR ("curr res psychol"[Journal] OR "crp"[All Fields]) OR ("c reactive protein"[MeSH Terms] OR ("c reactive"[All Fields] AND "protein"[All Fields]) OR "c reactive protein"[All Fields] OR "c reactive protein"[All Fields]) OR (("inter alpha inhibitor"[Supplementary Concept] OR "inter alpha inhibitor"[All Fields] OR "inter alpha inhibitor"[All Fields]) AND ("protein s"[All Fields] OR "proteinous"[All Fields] OR "proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])) OR ("phospholipases"[MeSH Terms] OR "phospholipases"[All Fields] OR "phospholipase"[All Fields] OR "phospholipasic"[All Fields]) OR ("bactericidal permeability increasing protein"[Supplementary Concept] OR "bactericidal permeability increasing protein"[All Fields]) OR "CD64"[All Fields] OR ("selenoproteins"[MeSH Terms] OR "selenoproteins"[All Fields] OR "selenoprotein"[All Fields]) OR ("lipopolysaccharide binding protein"[Supplementary Concept] OR "lipopolysaccharide binding protein"[All Fields] OR "lipopolysaccharide binding protein"[All Fields]) OR ("syndecans"[MeSH Terms] OR "syndecans"[All Fields] OR "syndecan"[All Fields]) OR ("plasminogen inactivators"[MeSH Terms] OR ("plasminogen"[All Fields] AND "inactivators"[All Fields]) OR "plasminogen inactivators"[All Fields] OR ("plasminogen"[All Fields] AND "activator"[All Fields] AND "inhibitor"[All Fields]) OR "plasminogen activator inhibitor"[All Fields]) OR (("plasminogen activators"[MeSH Terms] OR ("plasminogen"[All Fields] AND "activators"[All Fields]) OR "plasminogen activators"[All Fields] OR ("plasminogen"[All Fields] AND "activator"[All Fields]) OR "plasminogen activator"[All Fields]) AND "inhibito"[All Fields]) OR ("thrombomodulin"[MeSH Terms] OR "thrombomodulin"[All Fields] OR "thrombomoduline"[All Fields] OR "thrombomodulins"[All Fields]) OR ("fibrinogen"[MeSH Terms] OR "fibrinogen"[All Fields] OR "fibrinogens"[All Fields] OR "fibrinogen s"[All Fields] OR "fibrinogene"[All Fields]) OR ("angiopoietins"[MeSH Terms] OR "angiopoietins"[All Fields] OR "angiopoietin"[All Fields]) OR ("adrenomedullin"[MeSH Terms] OR "adrenomedullin"[All Fields] OR "adrenomedullins"[All Fields]) OR ("azu1 protein human"[Supplementary Concept] OR "azu1 protein human"[All Fields] OR "heparin binding protein"[All Fields]) OR ("fibrin fragment d"[Supplementary Concept] OR "fibrin fragment d"[All Fields] OR "d dimer"[All Fields]) OR ("chitinase 3 like protein 1"[MeSH Terms] OR "chitinase 3 like protein 1"[All Fields] OR "ykl 40"[All Fields]) OR ("copeptin"[All Fields] OR "copeptine"[All Fields]) OR ("intercellular adhesion molecule 1"[MeSH Terms] OR ("intercellular"[All Fields] AND "adhesion"[All Fields] AND "molecule 1"[All Fields]) OR "intercellular adhesion molecule 1"[All Fields] OR "icam 1"[All Fields]) OR ("lithostathine"[MeSH Terms] OR "lithostathine"[All Fields] OR ("pancreatic"[All Fields] AND "stone"[All Fields] AND "protein"[All Fields]) OR "pancreatic stone protein"[All Fields]) OR ("neopterin"[MeSH Terms] OR "neopterin"[All Fields] OR "neopterine"[All Fields] OR "neopterins"[All Fields]) OR ("macrophage migration inhibitory factors"[MeSH Terms] OR ("macrophage"[All Fields] AND "migration inhibitory"[All Fields] AND "factors"[All Fields]) OR "macrophage migration inhibitory factors"[All Fields] OR ("macrophage"[All Fields] AND "migration"[All Fields] AND "inhibitory"[All Fields] AND "factor"[All Fields]) OR "macrophage migration inhibitory factor"[All Fields]) OR ("High-mobility"[All Fields] AND "group-box"[All Fields] AND "1"[All Fields] AND ("protein s"[All Fields] OR "proteinous"[All Fields] OR "proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])) OR "Endocan"[All Fields] OR ("pentraxin"[All Fields] OR "pentraxins"[All Fields]) OR ("hepcidin s"[All Fields] OR "hepcidine"[All Fields] OR "hepcidins"[MeSH Terms] OR "hepcidins"[All Fields] OR "hepcidin"[All Fields]) OR ("calprotectine"[All Fields] OR "leukocyte l1 antigen complex"[MeSH Terms] OR ("leukocyte"[All Fields] AND "l1"[All Fields] AND "antigen"[All Fields] AND "complex"[All Fields]) OR "leukocyte l1 antigen complex"[All Fields] OR "calprotectin"[All Fields])) AND ("randomiz*"[All Fields] OR ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]))	1,988
44	RANDOMIZ* OR (CLINICAL TRIAL)	Most Recent	"randomiz*"[All Fields] OR "clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]	1,595,094
43	#9 AND #42	Most Recent	("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields] OR ("bronchopneumonia"[MeSH Terms] OR "bronchopneumonia"[All Fields] OR "bronchopneumonias"[All Fields] OR "bronchopneumoniae"[All Fields]) OR "CAP"[All Fields] OR "HAP"[All Fields] OR "VAP"[All Fields] OR ("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR ("acute"[All Fields] AND "respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "acute respiratory distress syndrome"[All Fields]) OR ("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR "ards"[All Fields])) AND ("procalcitonin"[MeSH Terms] OR "procalcitonin"[All Fields] OR "procalcitonine"[All Fields] OR "SUPAR"[All Fields] OR (("solubility"[MeSH Terms] OR "solubility"[All Fields] OR "solubilities"[All Fields] OR "soluble"[All Fields] OR "solubles"[All Fields] OR "solublization"[All Fields] OR "solublize"[All Fields] OR "solublized"[All Fields]) AND ("receptors, urokinase plasminogen activator"[MeSH Terms] OR ("receptors"[All Fields] AND "urokinase"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "urokinase plasminogen activator receptors"[All Fields] OR ("urokinase"[All Fields] AND "receptor"[All Fields]) OR "urokinase receptor"[All Fields])) OR ("interleukine"[All Fields] OR "interleukines"[All Fields] OR "interleukins"[MeSH Terms] OR "interleukins"[All Fields] OR "interleukin"[All Fields]) OR ("curr res psychol"[Journal] OR "crp"[All Fields]) OR ("c reactive protein"[MeSH Terms] OR ("c reactive"[All Fields] AND "protein"[All Fields]) OR "c reactive protein"[All Fields] OR "c reactive protein"[All Fields]) OR (("inter alpha inhibitor"[Supplementary Concept] OR "inter alpha inhibitor"[All	24,409

			Fields] OR "inter alpha inhibitor"[All Fields]) AND ("protein s"[All Fields] OR "proteinous"[All Fields] OR "proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])) OR ("phospholipases"[MeSH Terms] OR "phospholipases"[All Fields] OR "phospholipase"[All Fields] OR "phospholipasic"[All Fields])) OR ("bactericidal permeability increasing protein"[Supplementary Concept] OR "bactericidal permeability increasing protein"[All Fields]) OR "CD64"[All Fields] OR ("selenoproteins"[MeSH Terms] OR "selenoproteins"[All Fields] OR "selenoprotein"[All Fields]) OR ("lipopolysaccharide binding protein"[Supplementary Concept] OR "lipopolysaccharide binding protein"[All Fields] OR "lipopolysaccharide binding protein"[All Fields]) OR ("syndecans"[MeSH Terms] OR "syndecans"[All Fields] OR "syndecan"[All Fields]) OR ("plasminogen inactivators"[MeSH Terms] OR ("plasminogen"[All Fields] AND "inactivators"[All Fields]) OR "plasminogen inactivators"[All Fields] OR ("plasminogen"[All Fields] 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("macrophage"[All Fields] AND "migration"[All Fields] AND "inhibitory"[All Fields] AND "factor"[All Fields]) OR "macrophage migration inhibitory factor"[All Fields]) OR ("High-mobility"[All Fields] AND "group-box"[All Fields] AND "1"[All Fields] AND ("protein s"[All Fields] OR "proteinous"[All Fields] OR "proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])) OR "Endocan"[All Fields] OR ("pentraxin"[All Fields] OR "pentraxins"[All Fields]) OR ("hepcidin s"[All Fields] OR "hepcidine"[All Fields] OR "hepcidins"[MeSH Terms] OR "hepcidins"[All Fields] OR "hepcidin"[All Fields]) OR ("calprotectine"[All Fields] OR "leukocyte l1 antigen complex"[MeSH Terms] OR ("leukocyte"[All Fields] AND "l1"[All Fields] AND "antigen"[All Fields] AND "complex"[All Fields]) OR "leukocyte l1 antigen complex"[All Fields] OR "calprotectin"[All Fields])	
42	#10 or #11 OR #12 OR #13 or #14 OR #15 OR #16 or #17 OR #18 OR #19 OR #20 or #21 OR #22 OR #23 or #24 OR #25 OR #26 or #27 OR #28 OR #29 OR #30 or #31 OR #32 OR #33 or #34 OR #35 OR #36 or #37 OR #38 OR #39 OR #40 OR #41	Most Recent		746,488
41	calprotectin	Most Recent	"calprotectine"[All Fields] OR "leukocyte l1 antigen complex"[MeSH Terms] OR ("leukocyte"[All Fields] AND "l1"[All Fields] AND "antigen"[All Fields] AND "complex"[All Fields]) OR "leukocyte l1 antigen complex"[All Fields] OR "calprotectin"[All Fields]	6,735
40	hepcidin	Most Recent	"hepcidin s"[All Fields] OR "hepcidine"[All Fields] OR "hepcidins"[MeSH Terms] OR "hepcidins"[All Fields] OR "hepcidin"[All Fields]	5,676
39	Pentraxin	Most Recent	"pentraxin"[All Fields] OR "pentraxins"[All Fields]	2,492
38	Endocan	Most Recent	"Endocan"[All Fields]	498
37	High-mobility group-box 1 protein	Most Recent	"High-mobility"[All Fields] AND "group-box"[All Fields] AND "1"[All Fields] AND ("protein s"[All Fields] OR "proteinous"[All Fields] OR "proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])	5,923
36	Macrophage migration inhibitory factor	Most Recent	"macrophage migration inhibitory factors"[MeSH Terms] OR ("macrophage"[All Fields] AND "migration inhibitory"[All Fields] AND "factors"[All Fields]) OR "macrophage migration inhibitory factors"[All Fields] OR ("macrophage"[All Fields] AND "migration"[All Fields] AND "inhibitory"[All Fields] AND "factor"[All Fields]) OR "macrophage migration inhibitory factor"[All Fields]	5,333
35	neopterin	Most Recent	"neopterin"[MeSH Terms] OR "neopterin"[All Fields] OR "neopterine"[All Fields] OR "neopterins"[All Fields]	3,860
34	pancreatic stone protein	Most Recent	"lithostathine"[MeSH Terms] OR "lithostathine"[All Fields] OR ("pancreatic"[All Fields] AND "stone"[All Fields] AND "protein"[All Fields]) OR "pancreatic stone protein"[All Fields]	632

33	icam-1	Most Recent	"intercellular adhesion molecule 1"[MeSH Terms] OR ("intercellular"[All Fields] AND "adhesion"[All Fields] AND "molecule 1"[All Fields]) OR "intercellular adhesion molecule 1"[All Fields] OR "icam 1"[All Fields]	30,299
32	copeptin	Most Recent	"copeptin"[All Fields] OR "copeptine"[All Fields]	1,353
31	YKL-40	Most Recent	"chitinase 3 like protein 1"[MeSH Terms] OR "chitinase 3 like protein 1"[All Fields] OR "ykl 40"[All Fields]	1,842
30	d-dimer	Most Recent	"fibrin fragment d"[Supplementary Concept] OR "fibrin fragment d"[All Fields] OR "d dimer"[All Fields]	16,737
29	Heparin-binding protein	Most Recent	"azu1 protein human"[Supplementary Concept] OR "azu1 protein human"[All Fields] OR "heparin binding protein"[All Fields]	715
28	adrenomedullin	Most Recent	"adrenomedullin"[MeSH Terms] OR "adrenomedullin"[All Fields] OR "adrenomedullins"[All Fields]	3,990
27	angiopoietin	Most Recent	"angiopoietins"[MeSH Terms] OR "angiopoietins"[All Fields] OR "angiopoietin"[All Fields]	8,100
26	fibrinogen	Most Recent	"fibrinogen"[MeSH Terms] OR "fibrinogen"[All Fields] OR "fibrinogens"[All Fields] OR "fibrinogen s"[All Fields] OR "fibrinogene"[All Fields]	69,737
25	Thrombomodulin	Most Recent	"thrombomodulin"[MeSH Terms] OR "thrombomodulin"[All Fields] OR "thrombomoduline"[All Fields] OR "thrombomodulins"[All Fields]	5,450
24	Plasminogen activator inhibito - Spellcheck off	Most Recent	("plasminogen activators"[MeSH Terms] OR ("plasminogen"[All Fields] AND "activators"[All Fields]) OR "plasminogen activators"[All Fields] OR ("plasminogen"[All Fields] AND "activator"[All Fields]) OR "plasminogen activator"[All Fields]) AND "inhibito"[All Fields]	0
23	plasminogen activator inhibitor	Most Recent	"plasminogen inactivators"[MeSH Terms] OR ("plasminogen"[All Fields] AND "inactivators"[All Fields]) OR "plasminogen inactivators"[All Fields] OR ("plasminogen"[All Fields] AND "activator"[All Fields] AND "inhibitor"[All Fields]) OR "plasminogen activator inhibitor"[All Fields]	20,739
22	SYNDECAN	Most Recent	"syndecans"[MeSH Terms] OR "syndecans"[All Fields] OR "syndecan"[All Fields]	4,642
21	Lipopolysaccharide-binding protein	Most Recent	"lipopolysaccharide binding protein"[Supplementary Concept] OR "lipopolysaccharide binding protein"[All Fields] OR "lipopolysaccharide binding protein"[All Fields]	1,790
20	SELENOPROTEIN	Most Recent	"selenoproteins"[MeSH Terms] OR "selenoproteins"[All Fields] OR "selenoprotein"[All Fields]	25,064
19	CD64	Most Recent	"CD64"[All Fields]	1,606
18	Bactericidal/permeability increasing protein	Most Recent	"bactericidal permeability increasing protein"[Supplementary Concept] OR "bactericidal permeability increasing protein"[All Fields]	811
17	phospholipase	Most Recent	"phospholipases"[MeSH Terms] OR "phospholipases"[All Fields] OR "phospholipase"[All Fields] OR "phospholipasic"[All Fields]	65,395
16	Inter-alpha inhibitor proteins	Most Recent	("inter alpha inhibitor"[Supplementary Concept] OR "inter alpha inhibitor"[All Fields] OR "inter alpha inhibitor"[All Fields]) AND ("protein s"[All Fields] OR "proteinous"[All Fields] OR "proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])	530
15	c-reactive protein	Most Recent	"c reactive protein"[MeSH Terms] OR ("c reactive"[All Fields] AND "protein"[All Fields]) OR "c reactive protein"[All Fields] OR "c reactive protein"[All Fields]	100,652
14	crp	Most Recent	"curr res psychol"[Journal] OR "crp"[All Fields]	64,544
13	interleukin	Most Recent	"interleukine"[All Fields] OR "interleukines"[All Fields] OR "interleukins"[MeSH Terms] OR "interleukins"[All Fields] OR "interleukin"[All Fields]	407,912
10	procalcitonin	Most Recent	"procalcitonin"[MeSH Terms] OR "procalcitonin"[All Fields] OR "procalcitonine"[All Fields]	8,966
12	soluble urokinase receptor	Most Recent	("solubility"[MeSH Terms] OR "solubility"[All Fields] OR "solubilities"[All Fields] OR "soluble"[All Fields] OR "solubles"[All Fields] OR "solublization"[All Fields] OR "solublize"[All Fields] OR "solublized"[All Fields]) AND ("receptors, urokinase plasminogen activator"[MeSH Terms] OR ("receptors"[All Fields] AND "urokinase"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "urokinase plasminogen activator receptors"[All Fields] OR ("urokinase"[All Fields] AND "receptor"[All Fields]) OR "urokinase receptor"[All Fields])	1,200
11	SUPAR	Most Recent	"SUPAR"[All Fields]	915
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	Most Recent	"pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields] OR ("bronchopneumonia"[MeSH Terms] OR "bronchopneumonia"[All Fields] OR "bronchopneumonias"[All Fields] OR "bronchopneumoniae"[All Fields]) OR "CAP"[All Fields] OR "HAP"[All Fields] OR "VAP"[All Fields] OR ("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR ("acute"[All Fields] AND "respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "acute respiratory distress syndrome"[All Fields]) OR ("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR "ards"[All Fields])	574,923
7	ARDS	Most Recent	"respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR "ards"[All Fields]	62,572
6	acute respiratory distress syndrome	Most Recent	"respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR ("acute"[All Fields] AND "respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "acute respiratory distress syndrome"[All Fields]	59,709
5	VAP	Most Recent	"VAP"[All Fields]	6,138
4	HAP	Most Recent	"HAP"[All Fields]	7,169
3	CAP	Most Recent	"CAP"[All Fields]	56,788
2	bronchopneumonia	Most Recent	"bronchopneumonia"[MeSH Terms] OR "bronchopneumonia"[All Fields] OR "bronchopneumonias"[All Fields] OR "bronchopneumoniae"[All Fields]	6,726
1	pneumonia	Most Recent	"pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields]	463,230