European Journal of Internal Medicine 23 (2012) 429–435

Contents lists available at SciVerse ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review article

The role of biomarkers in low respiratory tract infections ☆

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ARTICLE INFO

Available online 26 May 2012

Keywords:
Biomarker
Procalcitonin
C-reactive protein
Proadrenomedullin
Pneumonia
COPD

ABSTRACT

Low respiratory tract infections (LRTI) represent the leading infectious cause of death worldwide and account for substantial use of healthcare resources. Physicians must adopt practices focused on improving outcomes and serum biomarker can help them in the management of patients with LRTI. Several studies have been carried out or are currently ongoing to evaluate the role of various biomarkers for the differential diagnosis, definition of prognosis, treatment and duration of antibiotic therapy in respiratory infections. The objective of this position paper of the Italian Society of Respiratory Diseases (SIMER) is to provide evidence-based recommendations for the use of biomarkers in routine clinical practice in the management of adult patients with LRTI. These guidelines capture the use of biomarkers both outside and inside the hospital, focused on community-acquired pneumonia, acute exacerbations of chronic obstructive pulmonary disease, hospital-acquired and ventilator-acquired pneumonia.

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1. Introduction

Low respiratory tract infections (LRTI), including pneumonia and acute exacerbation of chronic obstructive pulmonary disease (E-COPD), are one of the most common diagnoses in both outpatient and inpatient settings [1]. They represent one of the leading infectious causes of death worldwide and account for substantial use of healthcare resources [2,3]. Up to 30% of patients with community-acquired pneumonia (CAP) require hospitalization and 20% are admitted to an intensive care unit [4,5]. LRTI are also widely recognized as the most frequent and prevalent source of sepsis [6].

Due to the burden of LRTI on morbidity and mortality, healthcare providers must adopt practices focused on improving outcomes. Blood biomarkers such as white blood cells (WBC), C-reactive protein (CRP) or procalcitonin (PCT), mirroring the host response to infection, are currently used in clinical practice to improve the clinical management of patients with LRTI. A number of studies have been carried out or are currently ongoing to evaluate the role of various biomarkers for the differential diagnosis, definition of prognosis, treatment and duration of antibiotic therapy in respiratory infections. This is related to the great deal of uncertainty in the management of LRTI. The definition of the presence, the etiology and the severity of LRTI, as well as the treatment choice and duration, are frequently important challenges for the treating physician. Clinical features are sometimes misleading and not specific varying according to the etiology, bacterial or viral, adequacy of host response and presence of concomitant diseases. There is a clear need for diagnostic and prognostic biomarkers in LRTI.

The objective of this position paper of the Italian Society of Respiratory Diseases (Società Italiana di MEdicina Respiratoria, SIMER) is to provide evidence-based recommendations for the use of biomarkers in routine clinical practice in the management of adult patients with LRTI. The target audience for this guideline is, thus, all those whose routine practice include the management of adult LRTI.

This document is mainly based on clinical questions regarding the use of biomarkers in the management of LRTI. The guideline captures the use of biomarkers both outside and inside the hospital, focused on community-acquired pneumonia, acute exacerbations of chronic obstructive pulmonary disease, hospital-acquired and ventilator-acquired pneumonia. It contains graded recommendations and background information for each recommendation with details about cited reference and the evidence grades.

2. Materials and methods

A systematic literature search was performed to retrieve relevant publications from 1995 through to the present, which critically appraised and rated the pertinent clinical evidence, summarized

☆ No personal or financial support or author involvement with organization(s) with financial interest in the subject matter or any actual or potential conflict of interest exists.

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doi:10.1016/j.ejim.2012.05.002

these ratings in levels of evidence, and translated the best available evidence into graded clinical recommendations, see Appendices A, B, C, and D.

The following search terms were included in the literature search: biomarker, calcitonin, C-reactive protein (mp [multiple posting, in which the term appears in the title, abstract, or subject heading]), chronic obstructive pulmonary disease (exp), pneumonia (exp), or respiratory tract infections (exp). We restricted the search to studies performed only in adults. We included articles in English. We also identified relevant systematic reviews, meta-analyses, and controlled clinical trials and we reviewed their references.

The following text is a summary of the recommendations themselves and a discussion of the evidence on which the recommendations are based, under the following sections: 1) "Are serum/plasma biomarkers useful for LRTI diagnosis?"; 2) "Are serum/plasma biomarkers useful prognostic, severity and site-of-care indicators in LRTI?"; 3) "Are serum/plasma biomarkers useful treatment indicators in LRTI?"; 4) "Are serum/plasma biomarkers useful to guide duration of antibiotic therapy in LRTI?".

3. Are serum/plasma biomarkers useful for LRTI diagnosis?

Biomarkers usefulness for LRTI diagnosing, and identifying particular disease entities amongst LRTI is still a matter of controversy, see Supplementary Material. CRP, according to some observational studies, may have some role in identifying patients with pneumonia. Significantly higher CRP values in definite CAP compared to healthy controls and suspected CAP has been reported by Almirall et al. [7]. The role of CRP as a possible tool in the differential diagnosis in adults with cough of duration <3 weeks was evaluated by Flanders et al. [8]. CRP levels correlated with the presence but not with severity of pneumonia. Using a threshold of >40 mg/L CRP sensitivity and specificity in identifying pneumonia were 70% and 90%, respectively. Low sensitivity and specificity of CRP in the differential diagnosis of LRTIs have been confirmed by Holm et al. [9]. CRP showed a sensitivity of 73% and a specificity of 65% for CAP identification. This study showed that only CRP levels of >100 mg/L can be useful marker for the presence of CAP. The same indication come from Stolz et al. who showed a 91% specificity of CRP at the cut-off value of 100 mg/L to predict radiological confirmed pneumonia reaches [10]. In summary, CRP has a limited value as a predictor of the presence of pneumonia and no prospective intervention studies are available.

Boussekey et al. and Polzin et al. failed to demonstrate that PCT can have a role in predicting the presence of CAP [11,12]. However, Muller at al. in a more recent evaluation of the role of highly sensitive CRP and PCT measurements showed a better discriminatory value of these biomarkers compared to clinical signs [13]. The authors propose a more rationale algorithm using a lower PCT threshold compared to the previous studies. In this study PCT showed a higher diagnostic accuracy in differentiating CAP from other diagnoses, as compared to high sensitivity CRP and total leukocyte count. Moreover, PCT had a good performance as a predictor of bacteremia.

In primary care setting, both procalcitonin and CRP were associated with radiographic pneumonia, bacterial infection, and subsequent hospitalization. However, neither PCT nor CRP positive predictive values were high enough to be useful in clinical practice [14].

PCT was also evaluated as a potential marker for early diagnosis of ventilator-associated pneumonia (VAP). Ramirez et al., in a cohort study of well-characterized patients with VAP, evaluated the potential role of sequential measurements of PCT and CRP [15]. PCT and CRP plasma levels were statistically higher in patients with confirmed VAP, PCT being the more accurate marker. The study also showed that PCT and CRP levels in bronchoalveolar lavage (BAL) cannot differentiate confirmed and not confirmed VAP. The combination of the simplified clinical pulmonary infection score and serum PCT was able to exclude all false-positive diagnosis of VAP thus resulting in 100% specificity. The utility of PCT levels to improve the early diagnosis of VAP has been evaluated in different studies. Due to the use of dissimilar thresholds the results were not consistent [16,17].

Another proposed potentially useful diagnostic tool for CAP and VAP is the soluble triggering receptor expressed by myeloid cell (sTREM). In 2004, Gibot et al. report on 148 patients suffering from suspected CAP or VAP and receiving mechanical ventilation [18]. sTREM was assessed in the BAL fluid and its levels were a better predictor for bacterial infection than CIPS, TNF-alfa and IL-1 levels. This study also confirmed that PCT was not a useful marker for pneumonia identification. A further study evaluated the presence of sTREM in exhaled ventilator condensate (EVC) and in BAL fluid from 23 patients clinically suspected of having VAP [19]. In contrast with the first report, sTREM levels in BAL fluid did not differ in the VAP subjects compared to the non-pneumonia controls. However, sTREM-1 was detected in the EVC from 11 of 14 subjects with VAP, but from only 1 of 9 subjects without VAP, and was significantly higher in the pneumonia patients. Another study tends to rule out the value of sTREM detection in BAL as a useful tool in VAP diagnosis [20]. 105 consecutive patients receiving mechanical ventilation and undergoing BAL were studied. Nineteen patients (18%) met definite microbiologic criteria for bacterial or fungal VAP and sTREM-1 sensitivity and specificity was inferior to clinical parameters for the diagnosis of VAP.

Serum sTREM-1 levels in 150 patients with pneumonia, COPD and asthma exacerbations and 62 healthy controls were analyzed by Puha et al. [21]. Pneumonia patients showed the highest level of sTREM-1 compared to COPD, asthma and controls. No relationship between sTREM-1 levels and intensive care unit admission, need for invasive ventilation and length of hospital stay was found. Serum sTREM showed a moderate but insufficient degree of accuracy as a surrogate marker for the need for antibiotics in lower respiratory tract infections.

A recent retrospective study on patients admitted to intensive care unit addresses the potential role of sTREM in BAL fluid as a diagnostic marker of VAP [22]. The study evaluated 207 mechanical ventilated patients, 90 with confirmed VAP. Patients were screened daily for VAP using clinical criteria, and BAL was performed on the day of clinical VAP suspicion. sTREM-1 levels were not discriminative for VAP with a ROC curve analysis showing an area under the curve of 0.58 (95% CI 0.50–0.65).

4. Are serum/plasma biomarkers useful prognostic, severity and site-of-care indicators in LRTI?

Severity, prognosis, and site of care assessment are important early steps in the management of patients with LRTI, since CAP and E-COPD have a major burden on patients' centered outcomes and healthcare resources. Notably, severity assessment is crucial for both primary and secondary care physicians to drive clinical decisions, such as the need for hospital admission, requirement for intravenous therapy and level of monitoring if admitted. Since routine clinical judgment alone is a poor predictor of disease severity, the use of biomarkers can be helpful. Supplementary Material summarizes the main published studies on the use of biomarkers in the evaluation of severity, prognosis, and site-of-care of LRTI.

Many studies have evaluated the role of biomarkers for the assessment of severity and prognosis of patients with LRTI. Stolz et al. [23], in a prospective study on 167 patients admitted for E-COPD did not find any correlation between CRP, and PCT levels and short term or long-term outcome of exacerbation, such as length of hospital stay, ICU length of stay, in-hospital and 6-month mortality. The authors, however, demonstrated that copeptine was predictive for long-term clinical failure independent of age, comorbidity, hypoxemia, and lung function impairment in multivariate analysis. Asiimwe et al. [24] failed to find a significant role of CRP in the prediction of in-hospital mortality in patients suffering from E-COPD, and Lacoma et al. [25] found no significant difference in terms of PCT, CRP, and

neopterin for patients that had to be readmitted for a new exacerbation. Finally, Rammaert et al. [26] found that PCT level was independently associated with increased risk for ICU mortality in patients with severe acute exacerbation of COPD requiring intubation and mechanical ventilation.

To date several biomarkers have been evaluated for the prediction of severity and prognosis in CAP, such as CRP, pro-adrenomedullin (ProADM), PCT, mid-regional pro-atrial natriuretic peptide (ANP), pancreatic stone protein (PSP)/regenerating protein (reg). In general, CRP failed to demonstrate a significant association with both severity and prognosis in many studies [11,27–30], with an AUC for ROC analysis varying between 0.59 and 0.63, results associated with a poor discriminatory value. Menéndez et al. [29] demonstrated, in a study that involved 453 patients with CAP, a role of CRP when added to severity score, such as the Pneumonia Severity Index (PSI), the CURB-65 and the CRB-65. However, even if the AUC of ROC analysis increased significantly, the amount of the improvement (0.3–0.6) is probably not clinically significant. Both PCT, and Pro-ADM showed in more studies to rise significantly with increasing severity of CAP, with levels higher in non-survivors that in survivors [11,27,28,30–34]. In this case as well, however, the AUC of ROC analysis focused on patients' prognosis never showed a good discriminatory value. Boeck et al. demonstrated, in patients with VAP, that serum PSP/reg is significantly associated with the sequential organ failure, with levels higher in non-survivors [35]. The highest AUC to predict mortality was 0.76 at day 7 (moderate discriminatory value).

We found only a study focused on the accuracy of biomarkers (CRP, PCT, and mid-regional pro-atrial natriuretic peptide, ANP) in assisting emergency physician deciding hospital admission for CAP with low risk of complication. Authors concluded that, in a selected population of CAP with low risk of complication, a single ANP measurement is more accurate than CRP and PCT to predict appropriate admission. However, the AUC of ROC analysis using ANP (0.76), even if significantly higher than those of CRP and PCT, has only a moderate discriminatory value with a limited clinical utility, mainly when the level of ANP is <135 pmol/L. Then again, the combination of PSI and ANP threshold did not prove to gain accuracy in predicting appropriate admission.

5. Are serum/plasma biomarkers useful treatment indicators in LRTI?

The reliability of several biomarkers, including CRP, WBC and s-TREM1 to guide antimicrobial therapy is limited by their protracted response with late peak levels and suboptimal specificity, especially in patients with systemic inflammation. Supplementary Material summarizes the evidence based on previous trials using biomarkers measurements to guide antibiotic use in patients with respiratory tract infections.

In a randomized controlled trial assessing the frequency of antibiotic prescription in general practice, a CRP rapid test seemed not to reduce the use of antimicrobial agents in 812 patients with respiratory infections [36]. Conversely, CRP testing by means of point of care device (i.e., finger prick test) resulted in antibiotic use reduction without compromising recovery in a randomized open trial involving 107 LRTI patients. Interestingly, the 72% of control patients filled their prescription compared with only the 23% ($p<0.001$) in the CRP assisted group [37]. A pilot cross-sectional Irish study including 120 LRTI patients has further suggested near-patient CRP testing as a promising strategy in clinical practice [38].

While for a long time routine CRP determination has been motivated more by the low cost, easy availability and historic practice than by its accuracy, many efforts have addressed usefulness of PCT testing as an effective guidance for a more judicious antibiotics use, mainly by individual tailoring and early discontinuation. In 2004, Christ-Crain et al. first described the utility of PCT measurements through a rapid and highly sensitive assay to guide therapy in LRTI patients in a prospective, cluster-randomized, controlled, single-blinded intervention trial (the ProRESP study) [39]. Overall, 243 emergency department (ED) patients were assigned standard care or PCT-guided treatment based on PCT serum concentrations. Overall, antibiotic use was reduced by 47% with a 52% cost reduction and similar and favorable clinical outcomes in the 97% of cases. A further prospective randomized open intervention trial exclusively involved 302 ED patients with X-ray evidence of CAP (the ProCAP study) [40]. PCT-guided therapy significantly reduced the total antibiotic exposure, the rate of antibiotic prescription and the whole duration of treatment. In line with these findings, Stolz et al. further found that the absolute risk of antibiotic exposure was reduced by 31% with a concomitant reduction of antibiotic prescription in 208 consecutive ED patients requiring hospitalization for E-COPD in a single-center randomized prospective controlled trial (the ProCOLD study) [41]. In addition, an open randomized multi-center non-inferiority trial involving 53 primary care physicians and 458 patients demonstrated that treatment based on PCT guidance reduced the use of antibiotics without increasing the restrictions experienced by patients by more than 1 day not affecting clinical outcomes. Overall antibiotic prescription was reduced by 72% with no significant changes in the duration of therapy [42]. Finally, in a more recent multi-center, randomized controlled trial (the ProHOSP study) including 1359 ED patients with mostly severe LRTI the antibiotic prescription rates were reduced from 88% to 75% for all LRTI, with an overall reduction of therapy length ranging between 26% and 39%. Antibiotic-associated adverse effects were less frequent in the PCT group [43]. Finally, a trend toward a reduction of the proportion of patients with asthma and E-COPD who would have received antibiotics based on different CRP or PCT cut-off levels, as compared to standard treatment strategies, was reported by Bafadhel et al. [44]. Literature data on PCT-guided antibiotic therapy for E-COPD have recently been reviewed by Tokman et al. [45].

In 1995, Smith RP et al. firstly suggested the use of CRP levels monitoring as a marker of treatment response in a small cohort of in-hospital CAP patients [46]. Similarly, a prospective hospital-based study further confirmed that, unlike tumor necrosis factor-α and interleukin-6, persistently high or rising levels of CRP were suggestive of treatment failure in 28 patients with suspected CAP [47]. Daily measurement of CRP levels was found to be a marker of good prognosis (sensitivity 0.75; specificity 0.85) in a cohort of 53 ICU patients with severe CAP [48]. However, as suggested by de Jager et al. a slower decline of CRP values may be observed despite the onset of an appropriate treatment regimen depending on the pathogen type involved [49]. Usefulness of early changes of both CRP and sTREM-1 levels has further been suggested to predict treatment response in a prospective single center study involving 58 CAP patients in Taiwan [50]. A delayed normalization of CRP levels, that is a decline of <60% in 3 days and of <90% in 7 days, has been associated with an increased risk of having received an inappropriate empirical antibiotic therapy regimen in a retrospective analysis of a multicenter prospective study including 289 hospitalized patients with severe CAP [51]. Similarly, early changes in CRP behavior have been suggested to provide information for discriminating treatment failure from slow responding pneumonia, as assessed in a prospective multicenter observational study [52]. In a larger prospective study including 453 patients, Menéndez et al. have shown that CRP and PCT levels on day 1 were the strongest predictors of early failure, while IL-6 and CRP on day 3 predicted a late failure. Both CRP and PCT showed moderate sensitivity with low positive predictive values and high negative predictive values, the highest diagnostic value being reached when used together [53]. A careful attention, however, has to be tailored to patients receiving antibiotics prior to hospital entrance, as CRP and PCT levels on admission may be affected, both of them being predictive of mortality exclusively in patients not previously treated [46,54]. Conversely, any influence played by corticosteroids still remains an issue of controversy. Indeed,

while there is evidence of a suppressive effect on CRP expression [51,55], Perren et al. have reported that the time-dependent decline of CRP and PCT levels is not influenced by steroids in CAP patients adequately treated [56].

Finally, looking at additional biomarkers, B-type natriuretic peptide (BNP) levels on presentation have been found to be significantly higher in cases experiencing treatment failure including death, empyema and relapse in the ProCAP study population. The prognostic accuracy of BNP was superior to CRP, WBC and PCT, but comparable to PSI, the cut-off of 274 pg/mL discriminates successfully treated from non-responding patients [28]. Similarly, in the same cohort of patients, levels of pro-ADM significantly correlated with disease severity. In addition, pro-ADM significantly improved the prognostic accuracy of PSI to predict failure [27].

Póvoa et al. in a cohort of 47 microbiology confirmed VAP patients found that the CRP level was 0.62 times the initial value in survivors on day 4 of antibiotic therapy while increased to 0.98 in non-survivors [57]. Similarly, Lisboa et al. showed that a serum CRP ratio of 0.8 at 96 h after the initiation of antibiotics was suggestive of treatment appropriateness in 68 intubated patients with monomicrobial VAP in a prospective study realized in two medical–surgical ICUs [58]. Conversely, no correlation of decreasing delta-CRP and delta-PCT with the adequacy of antibiotic treatment has been found on the basis of quantitative endotracheal aspirate results on day 0 in 75 VAP patients. However, decreasing levels of both biomarkers were respectively associated with a sevenfold and fourfold increase of survival [59].

6. Are serum/plasma biomarkers useful to guide duration of antibiotic therapy in LRTI?

An overuse of antibiotics in LRTI may lead to adverse events as well as an increase in development of bacterial resistance. Io order to decrease the emergence of resistance to antibiotics, one of the targets would be to reduce the inappropriate or unnecessarily prolonged use of antibiotics. During the past decade, a growing body of literature showed a possible role of biomarkers in helping physicians to discontinue antibiotic therapy. Several trials have been conducted focusing primarily on the outcomes of patients with or without the use of a biomarker-guided algorithms for antibiotic therapy, most of them involving procalcitonin. Supplementary Material summarizes the evidence based on previous trials, systemic review and meta-analysis using biomarkers measurements in patients with respiratory tract infections. Different settings have been involved, including primary care, emergency departments, medical and surgical intensive care units.

Two studies have suggested that serial serum PCT measurements may allow reduction of antibiotic exposure and shortening of therapy duration by 2 to 3.5 days for patients with sepsis or septic shock in the intensive care unit [60,61]. Hochreiter et al. studied 110 surgical patients, including 43 patients with pneumonia that were randomly assigned to either a PCT-guided or a standard antibiotic regimen [60]. Antibiotic therapy in the PCT-guided group was discontinued, if clinical signs and symptoms of infection improved and PCT decreased to <1 ng/mL or the PCT value was >1 ng/mL, but had dropped to 25 to 35% of the initial value over three days. In the control group antibiotic treatment was applied as standard regimen over eight days. Similarly, Nobre et al. analyzed a total of 68 septic patients and antibiotics were stopped when PCT levels had decreased 90% or more from the initial value (if clinicians agreed) but not before day 3 (if baseline PCT levels were <1 mg/L) or day 5 (if baseline PCT levels were ≥ 1 mg/L) [61]. In control patients, clinicians decided on the duration of antibiotic therapy based on empirical rules. Stolz et al. firstly analyzed 101 patients with VAP in a multi-center randomized controlled trial assessing the usefulness of the antibiotic discontinuation strategy according to PCT concentrations [62]. Overall, the duration of antibiotic therapy was reduced by 27% in the PCT group. PCT monitoring significantly increased the number of antibiotic-free-days alive 28 days after VAP onset. Interestingly, in none of these studies, adverse effects on the clinical outcome were recorded. A further randomized, multi-center, prospective, parallel-group, open-label effectiveness trial assessing the benefit of PCT to help clinicians start, continue or stop antibiotic therapy in patients with suspected bacterial infection admitted to the intensive care units has more recently been realized (the ProRATA study) [63]. The overall study population analyzed was composed of 621 patients, including 141 cases of VAP and 180 cases of CAP. In the PCT group, antibiotics were started based on predefined cut-off ranges of PCT levels (from <0.25 mg/L to ≥ 1 mg/L) while treatment discontinuation was encouraged when PCT concentrations were less than 80% of the peak value or when an absolute level of <0.5 mg/L was recorded. Infection was microbiologically confirmed in nearly the 70% of patients for whom empirical treatment was considered adequate in the 90% of cases. Despite the PCT algorithm was not applied in the 53% of patients included in the corresponding group, a 23% relative reduction in days of antibiotic exposure was observed during the 28 days after inclusion in these patients as compared with those in the control group. Antibiotic exposure was lower in all subgroups of patients of the PCT group, including those affected by nosocomial pneumonia (2.3 days), VAP (3.1 days) and CAP (3.3 days). No differences in clinical outcomes and mortality were recorded by the same time period. During the past years, different RCT were performed to assess the use of PCT in discontinuing antibiotic therapy in LRTI, and several systematic reviews and meta-analysis have been published [64-72].

Evaluating all of the evidence published so far, a marked reduction in antibiotic exposure could be detected in all different setting, diseases and study populations. A shorter duration of antibiotic therapy was found in moderate- and high-acuity patients, such as those with pneumonia and sepsis in both general ward and ICU setting. Furthermore, none of the trials reported an increase in adverse outcomes, including mortality rate, although only a subset of the trials were powered to detect changes in clinical outcomes. However, several issues need to be addressed. 1) One of the biggest concerning is that almost the totality of the study use PCT and no other biomarker-oriented approaches have been tested in discontinuing antibiotic therapy in LRTI. 2) From a methodological point of view, the quality of the different studies is various with only three trials being at low risk for bias [42,43,63]. Furthermore, it should be acknowledged that none of the studies focused on the use of biomarkers in determining the duration of antibiotic treatment in LRTI managed to mask physicians with respect to treatment allocation of patients. 3) We found a clinical heterogeneity in the studies that may account for some statistical heterogeneity, which could have affected the results. This heterogeneity was in regard to the setting where the study was performed and to the diseases that were evaluated. 4) Most of the studies came from Europe and especially Switzerland, which may not reflect the broader experience. 5) The PCT threshold varies significantly from study to study. The PCT-guided algorithms were very heterogeneous as well as the values of PCT cutoffs chosen to make therapeutic decisions. 6) Severely immunocompromised and neutropenic patients were mostly excluded from RCT and this could preclude the generalizability of the results. Further data are needed before biomarker-based algorithms should be considered the criterion standard of care.

7. Learning points/recommendations

- Are serum/plasma biomarkers useful for LRTI diagnosis?
  - Biomarkers seem of limited value in the differential diagnosis of LRTI (B3)
  - Biomarkers seem of limited value in the diagnosis of community-acquired pneumonia (B3)
  - Biomarkers seem of limited value in the diagnosis of ventilator-associated pneumonia (B3)
- Are serum/plasma biomarkers useful prognostic, severity and site-of-care indicators in LRTI?

- Biomarkers seem of limited value in the evaluation of severity of LRTI (B3)
- Biomarkers seem of limited value in the evaluation of prognosis of LRTI (B3)
- Biomarkers seem of limited value in the evaluation of site-of-care of CAP (B3)

3. Are serum/plasma biomarkers useful treatment indicators in LRTI?
   - PCT may be used as a complementary tool in LRTI for discriminating conditions for which the use of antibiotics is really necessary (A2)
   - Serial testing of PCT levels may be a successful strategy to monitor the clinical course, adjust the duration of antibiotic therapy and identify non-responders in severe infections (A2)
   - Daily monitoring of CRP levels may provide useful information to clinicians to identify non-responding patients (B3)
   - Near-to-patient CRP testing may help to reduce antibiotic prescription in patients with non-severe LRTI (B3)
4. Are serum/plasma biomarkers useful to guide duration of antibiotic therapy in LRTI?
   - PCT may be used in deciding discontinuation of antibiotic treatment in septic patients in a ICU setting (A2)
   - PCT may be used in deciding discontinuation of antibiotic treatment in patients with pneumonia (A2)
   - PCT may be used in deciding discontinuation of antibiotic treatment in patients with LRTI other than pneumonia (C2)

Conflict of interest

The authors state that they have no conflicts of interest.

Appendix A. Checklist for critical appraisal

Study objective
☐ Causal ☐ Descriptive
☐ Aetiology (causes & risk factors) ☐ Diagnosis
☐ Prevention ☐ Prognosis
☐ Treatment
☐ Harm

Type of design
Original patient data:
☐ Yes ☐ No
☐ Randomised trial ☐ Systematic Review / Meta-analysis
☐ Prospective cohort study ☐ Consensus statement
☐ Retrospective cohort study ☐ Guideline
☐ Case control study ☐ Other .....
☐ Case report or case series
☐ Other .....

Missing data *yes no not known*
a) > 10% missing data ☐ ☐ ☐
b) > 5% difference between groups for missing data ☐ ☐ ☐
c) Bias due to missing data
☐ Likely (only when yes for both items)
☐ Unlikely (all other combined responses)
☐ Very unlikely (only when no for both items)

Blinding *yes no not known*
a) Blinding for determinant status* ☐ ☐ ☐
* *risk factor, diagnostic test, treatment, prognostic indicator*
b) Blinding for outcome status**
** *disease, gold standard, effect, course/endpoint*
c) Bias due to (lack of) blinding
☐ Likely (only when no for both items)
☐ Unlikely (all other combined responses)
☐ Very unlikely (only when yes for both items)

Study_results *yes no*
- Numerical results are clear ☐ ☐
- Numerical results support a positive answer to clinical question ☐ ☐

Appendix B. Checklist for levels of evidence

B.1. Evidence levels (ranging from 1A + to 6C −)

1 Systematic reviews and meta-analyses (of study types under grade 2 or 3)
2 Randomized trials
3 Prospective cohort
4 Case control, cross-sectional, retrospective cohort
5 Case reports
6 Expert opinion, consensus

B.2. 1st suffix

A low risk of biased results (flaws very unlikely for both blinding and follow-up)
B moderate risk of biased results (flaws unlikely for both blinding and follow-up)
C high risk of biased results (flaws likely for either or both blinding and follow-up)

B.3. 2nd suffix

\+ Numerical results unequivocal support a positive answer to the research question (i.e. determinant–outcome relation of interest clearly established)
– Numerical results unequivocal not supportive for a positive answer to the research question (i.e. determinant–outcome relation of interest not established)
? Numerical results are unclear

Appendix C. Checklist for grading recommendations

C.1. Grades of recommendation (ranging from A1 to C4)

A Consistent evidence → Clear outcome
B Inconsistent evidence –> Unclear outcome
C Insufficient evidence –> Consensus

C.2. Suffix for recommendation grades

- For preventive and therapeutic intervention studies (incl. harm)
  1 Systematic review (SR) or meta-analysis (MA) of RCTs
  2 1 RCT, or > 1 RCT but no SR or MA
  3 1 cohort study, or > 1 cohort study but no SR or MA
  4 Else
- FOR other studies
  1 SR or MA of cohort studies
  2 1 cohort study, or > 1 cohort study but no SR or MA
  3 Else

Appendix D. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ejim.2012.05.002.

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