Mini Review

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Host-response biomarkers for the diagnosis of bacterial respiratory tract infections

https://doi.org/10.1515/cclm-2018-0682
Received June 28, 2018; accepted August 3, 2018; previously published online September 5, 2018

Abstract: Appropriate antibiotic treatment for respiratory tract infections (RTIs) necessitates rapid and accurate diagnosis of microbial etiology, which remains challenging despite recent innovations. Several host response-based biomarkers due to infection have been suggested to allow discrimination of bacterial and non-bacterial microbial RTI etiology. This review provides an overview of clinical studies that investigated the diagnostic performance of host-response proteomic biomarkers to identify RTI microbial etiology. Procalcitonin and C-reactive protein have been studied most extensively; whereof procalcitonin has demonstrated the strongest diagnostic performance compared to other biomarkers. Proadrenomedullin, soluble triggering receptor expressed on myeloid cells-1, neopterin and pentraxin-3 need more studies to confirm their diagnostic value. For syndecan-4 and lipocalin-2 currently insufficient evidence exists. Common limitations in several of the studies were the relatively small scale setting, heterogeneous patient population and the absence of statistical power calculation.

Keywords: biomarkers; diagnosis; etiology; immunoresponse; respiratory infections.

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Introduction

Respiratory tract infections (RTIs), particularly those affecting the lower respiratory tract, are major causes of hospitalization and mortality in children and adults [1]. RTIs can be of bacterial or viral origin, with a strong overlap in clinical signs and symptoms. Bacterial RTIs, compared to viral RTIs, often do not resolve spontaneously, thus requiring antibiotic treatment [2]. To this end, standard clinical practice initiates an empiric antibiotic treatment covering the most likely pathogens involved [1]. This empiric treatment often is applied for prolonged periods due to significant turnaround times of the current diagnostic approaches.

Current limitations of diagnostic tools translate into sub-optimal use of antibiotics. Clinicians may decide to continue empiric antibiotic therapy to mitigate the risk of false negative results associated with current diagnostics. A study in the US showed that 30% of pediatric patients without a confirmed bacterial infection still received antibiotics [3]. Unnecessary use of antibiotics will increase the risk of side effects and promote the development of antibiotic resistance. Improving diagnostic tools and biomarkers to support the diagnosis of bacterial RTIs is therefore highly relevant.

The identification of RTI microbial etiology is based on microbial culturing of biofluids and targeted techniques such as antigen testing and detection of pathogen DNA using polymerase chain reaction (PCR). The significant turnaround time of >48 h for microbiological cultures represents a known challenge. Other challenges include incorrect diagnostic conclusions due to colonization and limitations to the sensitivity to detect pathogens, especially with fastidious bacteria and during an ongoing antibiotic treatment [4]. PCR technologies to detect genetic material of pathogens in biofluids are rapidly developing as an important diagnostic tool for bacterial infections including RTIs [4]. The advantages of PCR technology include its sensitivity and specificity in the presence of ongoing antibiotic therapy, simultaneous detection of multiple pathogens using multiplex PCR, and improved turnaround times of 1–6 h [4]. Limitations include

intrinsic specificity to specific pathogens, the practical burden of processing samples for PCR analysis, and the possibility to lead to false-positive results associated with colonization [4].

Host- or immune-response biomarkers measured in blood and other biofluids are of interest as they may support rapid discrimination between bacterial and viral etiology in RTIs. While host-response biomarkers are unlikely to differentiate between pathogens at the level of specificity such as PCR, they may support discrimination of bacteria vs. viral infections and potentially large classes (e.g. Gram-negative or Gram-positive), which can thus support rapid elimination of antibiotic use when no bacterial etiology is present. In addition, longitudinal measurements of such biomarkers may potentially quantify treatment response or failure. We provide an overview of current clinical evidence that supports the use of host-response proteomic biomarkers to establish the microbial etiology in patients with suspected RTIs, focusing on studies with supporting microbiological evidence of RTI etiology.

Host response biomarkers to detect bacterial infections

An overview of identified host response biomarkers in RTI patients is provided in Table 1. This includes a brief description of the study design, study population, the biological matrix sampled to quantify the biomarkers, biomarkers' cut-off value and metrics to evaluate diagnostic performance of RTI etiology in terms of sensitivity, specificity and area under receiver operating curve (AUROC).

C-reactive protein

C-reactive protein (CRP) is well established as an inflammatory marker associated with infection but also other inflammatory conditions. CRP increases more extensively during bacterial than non-bacterial RTIs [19] and is regularly used in clinical practice for diagnosing RTI microbial etiology. CRP-guided diagnosis was shown to reduce initial antibiotic prescriptions by approximately 20% in a meta-analysis of 13 randomized controlled trials (RCTs) involving 10,005 adult RTI patients [15]. However, CRP remains a non-specific inflammatory biomarker with insufficient specificity and sensitivity for bacterial RTIs. Moreover, CRP levels might not reflect the bacterial disease load or disease progression accurately due to its relatively slower increase and decline rates (i.e. kinetics) in blood [20] compared to the bacterial load.

Procalcitonin

Procalcitonin levels in blood increase following bacterial infection and decline following adequate treatment with antibiotics [20]. Procalcitonin increases more extensively during bacterial than in viral RTIs and has a more responsive kinetic profile, potentially reflecting the bacterial disease progression compared to CRP [20, 21]. These advantages supported the use of procalcitonin as a bacterial infection diagnostic biomarker including RTIs to guide antibiotics initiation and termination [21].

Procalcitonin has been studied as an intervention biomarker in RCTs, where procalcitonin levels in blood determined the initiation and discontinuation of antibiotic treatment. Procalcitonin-guided antibiotic treatment protocols were associated with a decrease of 19% in the antibiotic prescription rate ($p < 0.0001$) and 30% in overall exposure days to antibiotics ($p < 0.0001$) in a recent systematic review and meta-analysis involving patients with acute respiratory infections [16]. Similar rates of treatment failure and length of ICU or hospital stay were found between the procalcitonin and the control groups. Interestingly, a lower 30-day morality rate ($p < 0.05$) and antibiotic side effects ($p < 0.0001$) were observed within the procalcitonin group. A meta-analysis based on two RCTs of 655 upper RTI patients showed that procalcitonin was associated with a decrease in the antibiotic prescription rate from 51% in the control group to 18% in the procalcitonin group [22]. No significant differences in clinical outcomes such as treatment failure, mortality or days with restricted activity were found between the procalcitonin and the control groups. Current challenges that limit application of PCT include the determination of optimal diagnostic cutoff values to diagnose bacterial RTIs, and the impact of various patient conditions on these values, which should be studied in stratified randomized clinical studies.

Proadrenomedullin

Proadrenomedullin serves as a biomarker for indirect quantification of adrenomedullin. Adrenomedullin plays a vital role in immune-modulation, and its serum level increases during bacterial and viral infections [23]. The evidence of proadrenomedullin to support the diagnosis of bacterial RTIs is inconsistent. One study with pediatric patients with complicated and bacteremia-associated

Table 1: Overview of studies focusing on host-response protein-based biomarkers.

Biomarker	Study	Study subjects	Study size	Biofluid/cut-off	AUROC [95% CI]	Sensitivity, %	Specificity, %
sTREM-1	[5][a]	Pediatrics (4 months–14 years) with CAP clinical signs	235 Bacteria 111 Viruses 87 No etiology	Blood ≥69.56 pg/mL	0.50 [0.45–0.56]	31.8	73.7
proADM				Blood ≥0.32 nmol/L	0.58 [0.52–0.63]	78.0	35.7
CRP				Blood ≥7.98 ng/mL	0.66 [0.61–0.71]	50.9	80.4
PCT				Blood ≥0.188 ng/mL	0.69 [0.63–0.75]	67.4	65.1
MR-proANP				Blood ≤59.1 pmol/L	0.52 [0.46–0.57]	76.1	33.1
sTREM-1	[6][a]	Adults with pulmonary aspiration pneumonia	75 Patients 13 Controls	BALF >250 pg/mL	0.87 [0.78–0.94]	65.8	91.9
				Plasma NA	0.51 [0.39–0.62]	NA	NA
Pentrexin-3	[7][b]	Adults with COPD exacerbation	142 Patients	Sputum 118 ng/mL	0.65 [0.52–0.78]	60	NA[d]
sTREM-1	[8][c]	ICU patients with VAP, CAP, HAP, pulmonary aspiration pneumonia	510 Patients	BALF 5–900 pg/mL	0.91 [0.88–0.93]	87.0	79.0
proADM	[9][b]	Pediatrics <16 years with CAP signs	88 11 Complicated	Serum >0.16 nmol/L	0.85 [0.80–0.90]	100.0	70
Copeptin				Serum >10 pmol/L	0.59 [0.30–0.88]	50	67.5
CRP				Serum >100 mg/L	0.85 [0.80–0.90]	100.0	70.5
sTREM-1	[10][a]	Adults with acute respiratory illness	34 Patients 34 Control	Plasma 19.53 pg/mL	0.77 [0.63–0.9]	82.6	63
CRP				Plasma 8.7 mg/mL	0.79 [0.66–0.9]	78	78
Neopterin	[11][a]	Adults with RTIs including CAP	561 Patients 100 Healthy adult controls	Serum	0.76 [0.69–0.82]	NA	NA
CRP					0.76 [0.7–0.83]		
Neopterin	[12][a]	Adult with lower RTI/CAP	139 Patients 146 Healthy adult controls	Serum >15 nmol/L	0.83 [0.79–0.87]	86.7	69.5
CRP				Serum >20 mg/L	0.84 [0.8–0.88]	87.8	62
PCT				Serum >0.1 μg/L	0.77 [0.72–0.82]	60.4	79.6
Pentrexin-3	[13][a]	Mechanically ventilated adults	82	BALF 1 ng/mL	0.82 [0.71–0.92]	92.0	60.0
		Patients with bacterial pneumonia	12 Proven bacterial 58 No pneumonia	BALF 7 ng/mL	0.83 [0.66–0.99]	75.0	88
Syndecan-4	[14][a]	Pediatrics (<14 years) with CAP signs	74 Bacterial 16 Viral 20 Unidentified etiology	Serum >7.25 ng/mL	0.54 [0.42–0.65]	31.1	86.1
Lipocalin-2				BALF 1.633 ng/mL	0.51 [0.40–0.63]	58.1	50

Table 1 (continued)

Biomarker	Study	Study subjects	Parameter, units	Parameter value
CRP	[15][c]	10,005 RTI patients	Antibiotic prescription rate, %	
			Control	62.5
			CRP	43.6[f]
PCT	[16][c]	6708 Acute RTI patients	Total antibiotic exposure, days	8.1
			Control (n = 3372)	5.7[g]
			PCT (n = 3336)	
			Initial antibiotic prescription rate, %	
			Control	86
			PCT	70[g]
			Antibiotic treatment duration, days	
			Control	9.4
			PCT	8[g]
MR-proANP	[17][b]	545 Patients with suspected lower RTI	Serum MR-proANP, pmol/L	
			RTI patient	72.7 [62.5–89.5]
			Adult healthy controls	138.0[f] [74.1–279.0]
			No bacteremia	130 [71.9–257.0]
			Bacteremia	253.5[f] [126.0–573.0]
Copeptin	[18][b]	545 Adults with CAP, COPD, bronchitis, or asthma	Serum copeptin, pmol/L	
			Healthy controls	5.0 [3.5–8.3]
			Patients	25.3[f] [11.5–47.2]
			No bacteremia	24.2[f] [2.1–385.0]
			Bacteremia	67.0 [2.5–247.0]
Neopterin	[12][a]	267 Patients with suspected lower RTI	Median serum neopterin, nmol/L	
			Viral RTI	30.5
			Bacterial RTI	18.7[e]
			Healthy controls	5.8[f]
Neopterin	[11][a]	561 Patients with febrile respiratory illness	Median serum neopterin, nmol/L	
			Viral RTI	25.2
			Bacterial RTI	13.3[g]
			Healthy controls	6.2[g]

AUROC, area under the receiving operating curve; CI, confidence interval; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; CAP, community acquired pneumonia; proADM, proadrenomedullin; CRP, C-reactive protein; PCT, procalcitonin; MR-proANP, midregional proatrial natriuretic peptide; BALF, brochoalveolar lavage fluid; NA, not available; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; VAP, ventilator-associated pneumonia; HAP, hospital-associated pneumonia; HCAP, healthcare associated pneumonia; RTI, respiratory tract infections. [a]Prospective, observational study. [b]Retrospective analysis. [c]Meta-analysis study. [d]Missing data in the original article. [e]<0.05, [f]<0.005, [g]<0.0005.

pneumonia vs. pleural empyema showed 100% sensitivity and could accurately distinguish between these patient groups (AUROC >0.85) with a sensitivity and specificity comparable to CRP [9]. However, no specific statistical power calculation was performed as this study was a secondary analysis. Another study that compared the utility of proadrenomedullin to predict bacterial community-acquired pneumonia (CAP) vs. non-bacterial RTIs did not show the predictive relevance of proadrenomedullin [5]. In summary, prospective studies with a larger and more uniform patient population can support establishing the relevance of proadrenomedullin in identifying bacterial etiology of RTIs.

sTREM-1

Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) levels rise in biofluids after an increase of TREM-1 expression on neutrophils, granulocytes, monocytes and alveolar macrophages in normal lung tissue [24]. TREM-1 regulates inflammatory responses associated with monocytes and neutrophils [24]. Microbial products increase TREM-1 expression with a subsequent increase of sTREM-1 levels in the biofluids [24].

A meta-analysis of nine studies showed that bronchoalveolar lavage fluid (BALF) sTREM-1 could identify bacterial RTIs with high accuracy [8]. BALF sTREM-1 was higher only in pneumonia patients with positive BALF cultures (100% specificity) and could accurately differentiate them from pneumonia patients with negative BALF cultures (AUROC > 0.85). Furthermore, BALF sTREM-1 outperformed plasma sTREM-1 that failed to distinguish both conditions [6]. However, another study in patients with respiratory insufficiency and bacterial infections only reported a moderate diagnostic performance [25]. For comparison of bacterial vs. viral CAP in pediatric patients, plasma sTREM-1 showed very low sensitivity [5]. In patients with bacterial and non-infectious lung infiltrates, serum sTREM-1 levels were reported to be highly sensitive and with moderate discriminatory power [10]. However, the control group of this study missed patients with lung infiltrates due to viral infections that are associated with elevated sTREM-1 levels [6, 8].

In conclusion, the choice of sTREM-1 biological matrix may be related to the accuracy of sTREM-1 diagnostic performance of microbial etiology; the results favor the use of BALF over serum sTREM-1. Despite inconsistency of sTREM-1 cutoff values, which might affect sensitivity and specificity with no real variation of accuracy [26], these results foster further investigation of BALF sTREM-1 diagnostic value in RTIs.

Pentraxin-3

Pentraxin-3 is an acute inflammatory marker and a vital component of innate immunity [27]. Pathogens stimulate pentraxin-3 production in different cells including epithelial, endothelial, myeloid dendritic cells, neutrophils and macrophages [27]. Pentraxin-3 promotes the recruitment of neutrophils [27].

Studies suggest the potential diagnostic value of pentraxin-3 in RTIs. Sputum pentraxin-3 levels were higher in chronic inflammatory pulmonary disease (COPD) patients with bacterial exacerbations compared to those with viral and non-infectious exacerbations [7]. However, COPD is an inflammatory state that could potentially affect levels of the inflammatory marker pentraxin-3, the effect of COPD *per se* on pentraxin-3 levels requires further investigation. BALF pentraxin-3 was associated with good performance and >90% sensitivity to discriminate patients with culture positive – bacterial, viral or fungal – and culture negative pneumonia at a cut-off of >1 ng/mL [13]. At a cut-off of >7 ng/mL, BALF pentraxin-3 performed similarly and identified the subgroup of patients with proven bacterial pneumonia. The non-homogenous patient population involving CAP, hospital-acquired pneumonia, health-care associated pneumonia and ventilator-associated pneumonia patients may have affected the sensitivity and specificity of BALF pentraxin-3.

Syndecan-4

Syndecan-4, a member of the heparin sulfate proteoglycans is ubiquitously present on many cells including alveolar macrophages and might play a role in RTIs [28]. Patients with mild acute pneumonia showed approximately 60% higher syndecan-4 levels compared to healthy controls, but also to patients with severe pneumonia [29]. Syndecan-4 levels declined gradually when the patients received adequate antibiotics. However, a limitation of this study was that a comparison of pneumonia patients to healthy volunteers was made without identifying the etiology of pneumonia, i.e. bacterial or viral. The conflicting difference between higher syndecan-4 levels in mild vs. severe pneumonia is unexpected and raises questions about the validity of the study findings. In another study in pediatric patients with bacterial or viral CAP, syndecan-4 showed poor discriminatory power (AUROC ≈ 0.5) [14]. However, the viral pneumonia subgroup in this study was underrepresented (16 patients) compared to the bacterial subgroup (74 patients). Therefore, more extensive studies, which are adequately powered and with

predefined microbial etiology of RTI patients involved, are required to further assess the relevance of this potential biomarker to bacterial RTI.

Lipocalin-2

Lipocalin-2 levels increase during infection and inflammation; lipocalin-2 plays a key role in innate immunity through interference with bacterial iron uptake [30]. In pediatric patients with bacterial and viral pneumonia, lipocalin-2 failed to discriminate between these groups (AUROC ≈ 0.5) [14]. Here, lipocalin-2 was studied in the same study as syndecan-4, which under-represented the viral pneumonia group. Therefore, more evidence is required to assess the diagnostic relevance of lipocalin-2 in RTIs.

Midregional proatrial natriuretic peptide

Midregional proatrial natriuretic peptide (MR-proANP) is a byproduct of atrial natriuretic peptide (ANP) biosynthesis, and is used as a surrogate for ANP quantification, which has a half-life as short as 4 min in contrast to the 90-min half-life of MR-proANP. ANP regulates macrophages activity in innate and acquired immunity [31].

MR-proANP has demonstrated low performance as a diagnostic biomarker of bacterial RTIs. In two studies of bacterial and non-bacterial RTIs pediatric patients, MR-proANP failed to differentiate between these two groups [5, 32]. However, in adult patients with lower RTIs, increased values for MR-proANP in comparison to adult healthy controls have been reported [17]. Furthermore, in this study, CAP patients had significantly higher MR-proANP levels than patients with other RTIs. RTI patients with bacteremia had higher MR-proANP levels than patients without bacteremia. However, MR-proANP showed low ability to discriminate between blood culture positive and negative adult mild CAP patients [33].

The current evidence does not support MR-proANP as a biomarker of bacterial RTIs. However, different study populations may have caused variation of MR-proANP levels among the studies as MR-proANP is also affected by age and heart conditions [34].

Copeptin

Copeptin, a more stable byproduct of vasopressin biosynthesis, serves as a biomarker of vasopressin quantification. Bacterial endotoxins induce an increase of vasopressin levels in blood [35]. The low *ex-vivo* stability and platelets binding limits vasopressin potential for quantification and use as a biomarker of RTI [35].

In pediatric patients with uncomplicated CAP and CAP complicated with bacteremia and/or empyema, copeptin was not identified as a relevant biomarker [9]. However, this is the same secondary analysis that investigated sTREM-1 and copeptin and was not associated with statistical power calculation. Another study showed that copeptin levels were significantly higher in adult patients with respiratory conditions including CAP, COPD, bronchitis and asthma compared comparison to healthy controls [18]. Particularly, copeptin was significantly higher in patients with positive blood cultures. However, the absence of microbiological evidence of RTI microbial etiology, – e.g. bacterial culture or PCR results – limits the results of these studies. Empyema and bacteremia are systemic infectious complications of RTIs; their presence or absence does not confirm or rule out bacterial RTIs in patients.

Neopterin: a pteridine biomarker

Neopterin is produced in monocytes and macrophages and represents a marker of cell-mediated immunity [36]. Neopterin serum levels increase during inflammation [36] and viral RTIs [11, 12]. Neopterin showed potential to diagnose a viral etiology of RTIs in two studies that compared healthy subjects, and bacterial and viral RTIs patients. Median serum neopterin levels in patients with viral RTIs were 200% higher compared to bacterial RTIs [11, 12]. However, both studies had the same study design and were performed in the same hospital in Hong Kong; multicenter studies could further confirm the relevance of neopterin to identify the microbial etiology of RTIs.

Discussion

Several host-response protein-based biomarkers have been investigated in the last decade to discriminate between bacterial and non-bacterial RTIs. Procalcitonin and CRP have been studied most extensively. Procalcitonin may have the strongest performance compared to other biomarkers. Proadrenomedullin, neopterin, sTREM-1 and pentraxin-3 warrant future studies to confirm their diagnostic value. The available evidence does not support the use of syndecan-4 and lipocalin-2 as biomarkers of bacterial or viral RTIs. Limitations in study design and sample

size limited for several biomarkers, the ability to draw meaningful conclusions.

The absence of a reliable sensitive and specific "gold standard" to support diagnosis of the microbial etiology of RTIs remains a major challenge in the interpretation of observational studies that aim to identify biomarkers. In our review, studies relied mainly on culture-based methods as a reference that have inadequate sensitivity [37], which further declines after the beginning of antibiotic therapy. Alternatively, more sensitive methods such as PCR and antigen testing are limited by the intrinsic specificity to pathogens and their inability to differentiate

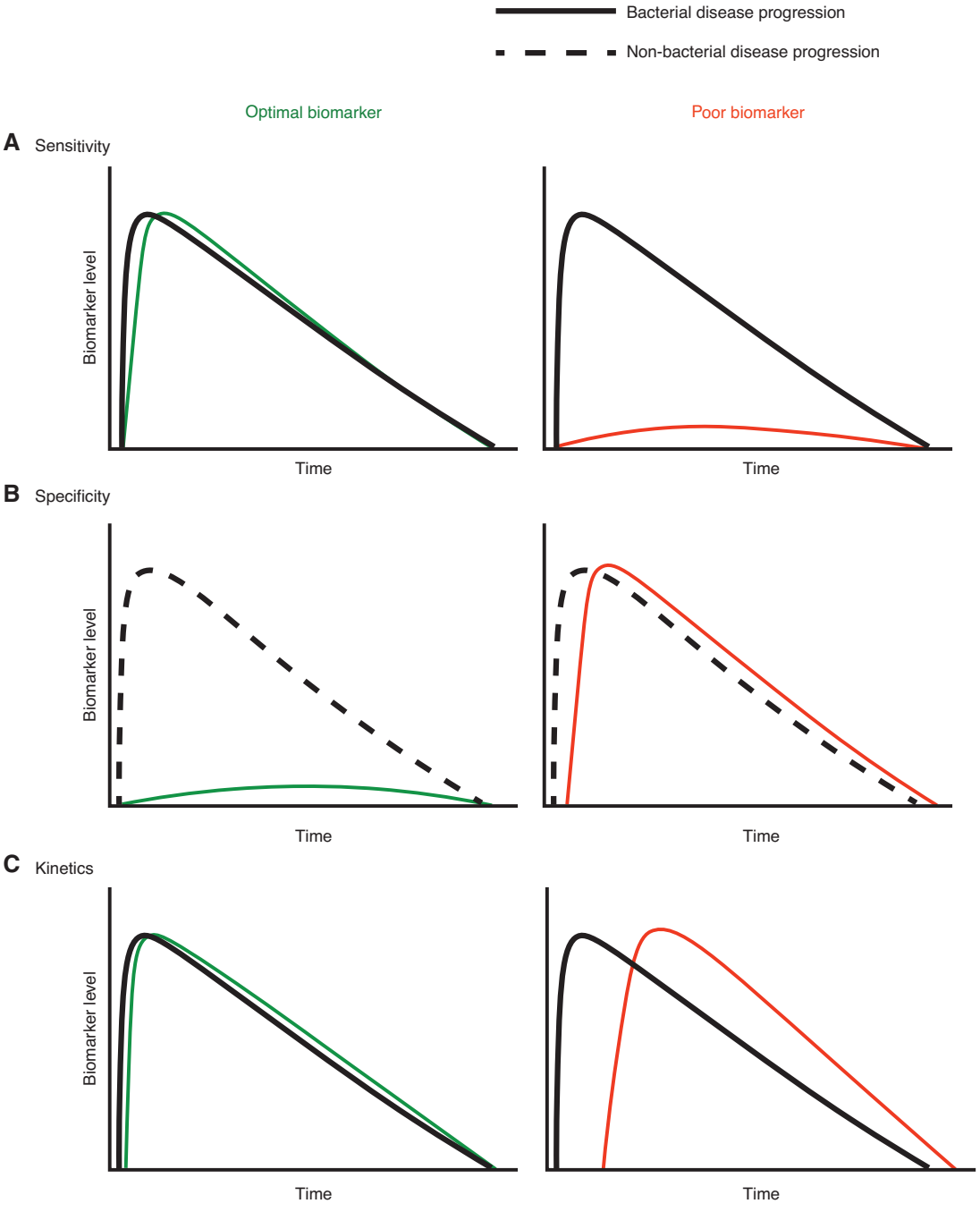

Figure 1: Considerations for an optimal diagnostic biomarker of bacterial RTIs.
(A) Correlation between biomarker and bacterial disease progression profile is important for specificity while (B) a lack of correlation between non-bacterial (e.g. viral) disease progression should be present. (C) The biomarkers should closely follow the kinetics of disease progression.

latent and active infections. Observational studies that investigate novel diagnostic biomarkers that only use a single "unreliable" reference test to support diagnosis are thus of limited value. Rather, multiple diagnostic approaches should be used in combination. The majority of studies reviewed employed multiple diagnostic techniques simultaneously, that included examining the patients' clinical presentation, radiology findings, biofluids culture, serology, urinary antigen testing and PCR to detect pathogenic DNA. Although these techniques identified the exact bacterial species in a considerable number of patients, a definite diagnosis often remains challenging to obtain [5]. In contrast, interventional studies directly evaluating the relationship between clinical outcomes and biomarkers may allow to more definitively identify infection biomarkers [38]. Particularly, head-to-head interventional studies biomarkers could prioritize biomarkers based on their relative diagnostic value. However, concerns over the patients' safety represent a persistent challenge for interventional research, which should be performed only after the reliability and robustness of a certain biomarker to identify RTI microbial etiology have been established in proof-of-concept observational studies.

The characterization of the sources of variation in individual biomarker concentrations will be crucial to improve diagnostic performance. This could be done through characterization of the effects of patient-specific factors such as age, gender, organ function and drug treatment and may be relevant to improve the current level of variation that may impair diagnostic performance [39]. Elderly and patients with cardiac morbidities show higher pro-ANP levels [34]. Steroids may lead to decreased baseline levels of inflammatory biomarkers. In one study, administering prednisone as an adjunct CAP treatment was associated with significantly lower CRP values. However, procalcitonin levels were not altered significantly [40]. Particular caution should be exercised when biomarkers are used to identify RTI etiology particularly in COPD patients who are on constant steroid treatment and are at-risk of RTIs. In addition, variation in individual biomarker concentrations may also be better understood by the consideration of the kinetic nature of these protein biomarkers in order to understand the relationship of the phase of the infections across individual patients, which may be very different (Figure 1). Baseline (i.e. pre-treatment) biomarker levels may provide information on probable RTI etiology guiding antibiotic initiation. The subsequent measurement of the concentrations of these biomarkers can provide further insight into the progression of the disease course, and after initiation of therapy may be used to evaluate treatment response and to identify patients with a poor treatment response or prognosis [41]. To this end, kinetic biomarker profiles can be used to reduce mortality and antibiotic-related side effects in RTI patients [16]. Thus, a desirable biomarker will demonstrate responsive kinetics; i.e. its level in biofluids increases and declines rapidly reflecting the disease load.

Diagnostic technologies such as PCR or MALDI-TOF that focus on molecular characterization of the pathogen, which is both a benefit and a limitation as these assays are highly sensitive and specific, but may in some cases detect irrelevant pathogens due to colonization or at irrelevant disease loads. In contrast, host-response biomarkers aim to identify the immunological host-pathogen response taking into consideration the association with the actual disease state. Host response biomarkers have a less selective profile with respect to specific molecular pathogen characteristics, i.e. until now are focused on classification of bacterial or viral infections. In parallel to the role of pathogen-focused diagnostics, host-response biomarkers may have a clinically relevant role to rapidly stratify patients and treatment.

The clinical studies in this review were restricted to the potential of host-response biomarkers to differentiate bacterial and nonbacterial RTIs. The potential of host-response biomarkers to classify etiology into major classes as Gram-positive or Gram-negative bacteria or more detailed bacterial species associated with RTIs has a large clinical potential and relevance, but remains to be investigated. This will potentially support narrowing the spectrum of the prescribed antibiotics but should follow establishing the potential of one of more of the biomarkers to identify patients with bacterial RTIs.

Combining several host-response biomarkers could be one way forward to improve diagnostic performance. For instance, the combinations of procalcitonin and proadrenomedullin increased the probability of diagnosing patients with bacterial RTIs from 0.91 to 0.98 [42]. Another two studies showed that CRP/neopterin and CRP*procalcitonin/neopterin ratios performed significantly better to differentiate adult patients with bacterial and viral RTIs compared to CRP, procalcitonin or neopterin alone [11, 12]. The latter two studies demonstrate the value of combining biomarkers that increase with bacterial RTIs like CRP and procalcitonin and a biomarker that increases with viral RTIs as neopterin.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: JGCvH and EvdG acknowledge support received grant from The Netherlands Organisation for Health Research and Development (ZonMW; Funder Id: 10.13039/501100001826, Project ID 541001007) to investigate novel biomarkers for respiratory tract infections. MAS, EMWvdG, JGCvH declare no conflicts of interest.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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