Review

Biomarkers and Predictor Models for Serious Bacterial Infections in Febrile Children

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Review

Biomarkers and Predictor Models for Serious Bacterial Infections in Febrile Children

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Abstract: Febrile infections are a common cause of presentation to the emergency department (ED) in children. While viral infections are usually self-limiting, sometimes bacterial illnesses may lead to sepsis and severe complications. Inflammatory biomarkers such as C reactive protein (CRP) and procalcitonin are usually the first blood exams performed in the ED to differentiate bacterial and viral infections; the better understanding of immunochemical pathways has nowadays led to the discovery of new and more specific biomarkers that could play a role in the emergency setting. The aim of this narrative review is to provide the most recent evidence on biomarkers and predictor models combining them for serious bacterial infections (SBI) diagnosis in febrile children. Literature analysis showed that inflammatory response is a complex mechanism in which many biochemical and immunological factors contribute to host response in SBI. CRP and procalcitonin still represent the most used biomarkers in the pediatric ED for the diagnosis of SBI. Their sensibility and sensitivity increase when combined and for this reason it is reasonable to take them both into consideration in the evaluation of a febrile children. The potential of machine learning tools, who represent a real novelty in medical practice, in conjunction with routine clinical and biological information, may improve accuracy of diagnosis and target therapeutic options in SBI. However, studies on this matter are not yet validated in younger populations, making their relevance in pediatric precision medicine still uncertain. More data from further researches are needed to improve clinical practice and decision making using these new technologies.

Keywords: biomarker; C reactive protein; interleukin; presepsin; procalcitonin; serious bacterial infection

1. Introduction

Febrile illness is a common pediatric presentation, accounting for 14-20% of attendances to the pediatric emergency department (ED) [1–3]. It is frequently the expression of an underlying infection, and a large proportion of these cases will be viral in origin, with a benign and self-limiting course. However, in a certain percentage of children, fever can be the manifestation of a bacterial infection which can be serious (as septicemia, meningitis, confirmed appendicitis, pneumonia, osteomyelitis, cellulitis, or complicated urinary tract infection) and the consequences of missing the diagnosis can potentially be catastrophic. Neonates and infants are at higher risk of serious bacterial infection (SBI) and may not display the same clinical features of infection and sepsis as older children, making the assessment more challenging. Distinguishing between a SBI requiring antibiotics and a viral infection is mostly a clinical decision and international evidence-based guidelines are a useful tool in that scenario [4,5].

Inflammatory biomarkers are usually the first investigations required in the ED which aid differentiating bacterial from nonbacterial infections in febrile infants and their result influences the subsequent case management. Stol et al. summarized the properties of the perfect biomarker for infections: has a positive test result in infected patient, has a negative test result in patients without an infection, distinguishes etiology, is independent of comorbidities, is a predictor of severity, is a predictor of outcome, is a quick and easy test with small variation coefficient, is affordable [6]. Currently no single biomarker has sufficient diagnostic accuracy to satisfy all these properties and the clinical context remains vital in the diagnostic and therapeutic process. In this review, we summarize the current knowledge about the role of biomarkers for SBI in children presenting with fever in the ED and we discuss the future perspective in this field. To this end, we conducted

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electronic research in the PubMed database from September 2018 to September 2023 to using “sepsis” OR “severe bacterial infection” AND “infant” OR “children” OR “pediatric” OR “paediatric" OR “biomarker” OR “blood culture” OR “blood cell count” OR “neutrophil count” OR “ANC” OR “C-reactive protein “ OR “CRP” OR “procalcitonin” OR “PCT” OR “inflammatory markers” OR “cytokine“ OR “IL-2” OR “IL-6” OR “IL-10” OR “IL-27” OR “soluble triggering receptor” OR “sTREM-1” OR “platelet” OR “TRAIL” OR “IP-10” OR “presepsin” as keywords. Only articles written in English were selected, and a manual search of the references of eligible articles was made.

2. Hematological biomarkers

2.1. White blood cell count (WBC) and absolute neutrophil count (ANC)

WBC and ANC have been widely used worldwide as predictors of SBI in febrile children. During a bacterial infection, neutrophils are rapidly recruited to infection sites where they evoke an immune response, bind, and ingest microorganisms by phagocytosis and kill microbes [7]. A larger number of neutrophils are consumed at the site of SBI, and they continue to be supplied to the infected site from the bone marrow via the bloodstream. Therefore, dynamic changes occur in WBC and ANC, that may reflect the real-time condition of a patient with bacterial infection. However, a recent systematic review and meta-analysis of diagnostic studies showed that the WBC offers a low sensitivity (58%) and a specificity of 73%, lower if comparted to procalcitonin (PCT) and C-reactive protein (CRP) analysis [8]. Similarly, a study that compared the WBC, ANC and CRP in relation to the onset of fever founded that CRP had a better sensitivity and specificity than either WBC or ANC, regardless of the duration of fever. Interestingly, in this study all biomarkers performed better with a duration of fever of >12 hours [9]. Van den Bruel et al. investigated the diagnostic value of laboratory tests for the diagnosis of SBI in febrile children in ambulatory settings founding that WBC probably provide some diagnostic value in ruling in serious infection, but less than PCT and PCR, and have no value at ruling it out [10].

2.2. Platelet indices

Studies have identified platelets as one of the first-line indicators in response to pathogens with participation to phagocytosis through proteins from their granules. Different platelet indices, such as PNLR (platelet-to-neutrophil/lymphocyte ratio), PNR (platelet-to-neutrophil ratio) and secreted proteins, such as sP-selectin, CXCL4, CXCL7 and serotonin have been studied as markers to discriminate viral and bacterial infection pathogenesis [11].

Considering children who access in ED with early onset of fever (<12 h), it has been observed a higher PNLR value in whose suffering from bacterial infections [12]. sP-selectin in ED may discriminate between septic and non-septic patients [12].

CXCL7 has a valid specificity and sensibility in detecting early signs of sepsis and excluding other causes of SIRS. CXCL7 and sP-selectin, alone and combined, are statistically significant to discriminate sepsis and bacterial infections from other diseases [13]. In pediatric patients in whom an acute infectious event is suspected CXCL4 and serotonin levels are not indicative in discriminating the etiology of the event in progress; CXCL4 has a role during the viral response and its elevation in blood stream is not significant in patients with sepsis or bacterial infections [14]. However, the values are not yet standardized in pediatric population and more studies are necessary to confirm normal values in healthy children and in different clinical conditions i.e. chronic inflammation, trauma, and acute infection [15]. CXCL7 and sP-selectin are promising for the future and the aim is to understand how to correlate early signs of infection to these biomarkers’ levels, improving the recognition of a bacterial infection from a viral one and contextually SBI [16].

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3. Inflammatory biomarkers

3.1. C-reactive protein (CRP)

CRP is currently one of the most frequently used biomarkers for infection in the ED worldwide. It is a short pentraxin, which is synthesized in the liver following stimulation by cytokines (IL-1beta, IL-6 and TNF-alfa) within 4–6 hours after tissue injury, doubling every 8 hours and peaking at 36-50 hours [17,18]. CRP plays an important role in host defense through complement activation via the classic pathway, modulation of the function of phagocytic cells, and increase in cell-mediated cytotoxicity [19].

A rise of CRP levels can be caused by conditions other than infections, for example trauma, malignancy, rheumatologic disorders, burns, pancreatitis, and periodic fever syndromes and CRP values should be interpreted cautiously in these cases [20]. On the contrary, suppressed levels of CRP can be present in liver failure and immunocompromise patients [21]. Nevertheless, several studies demonstrate the utility of CRP for early identification of febrile children at risk for SBI [10].

A recent systematic review and meta-analysis evaluated the diagnostic value of CRP for early identification of young children at risk for SBI among those presenting with fever without source, founding that overall sensitivity was 0.74 (95% confidence interval [CI], 0.65 to 0.82) and overall specificity was 0.76 (95% CI, 0.70 to 0.81) [8].

A crucial dilemma in clinical practice is the threshold to use for the identification of SBI. A very low cut-off value will be very sensitive but poorly specific and a very high cut-off will be specific but poorly sensitive [21]. In a recent study by Verbakel et al., the cut-off value of 75 mg/L has been suggested as highlighting those children at greater risk of SBI and a CRP cut-off of 20 mg/L was suggested as being useful in identifying children at low risk of SBI [22]. CRP value must be interpreted with caution when fever has been present <12 h based on the kinetics of this biological marker [9].

Studies showed that high levels of CRP and PCT are strongly predictive of SBI in children with fever, independent of duration of disease; on the contrary, low CRP levels should not be used to rule out or confirm SBI in children with a short duration of fever and PCT seems superior to CRP in detecting SBI at an earlier stage of the disease [9,23,24].

Neonates and infants <3 months deserve specific considerations [25]. A large multicentered European study of over 2000 infants under 3 months of age admitted to a pediatric ED with fever without source found that CRP was a poor predictor of SBI [26]. A 70 mg/L cut-off had a specificity of 93.8%, but sensitivity of only 69.6%. In this study, CRP value was higher than WBC and ANC in detecting bacteremia, but the most accurate predictor of SBI was appearing unwell [26]. Similarly, one large multicentered American study of suspected sepsis in neonates found the initial CRP value to be poorly sensitive for SBI [27]. However, they reported that an elevated CRP >10 mg/L at 24–48 hours after presentation demonstrated a 97.6% and 94.4% sensitivity for proven (culture positive) or probable (clinical features but no positive cultures) bacterial infection, making serial CRP measurements more accurate in diagnosing SBI in neonates.

3.2. Procalcitonin

Procalcitonin (PCT) is a 116 – amino acid protein precursor for calcitonin produced by parafollicular cells [28]. In normal conditions serum levels of PCT are lower than 0.05 ng/mL, while during SBI they can increase up to 700 ng/L [29]. During SBI, the site of PCT production is not limited to the neuroendocrine cells. The release of PCT is induced by increasing the CALC1 gene expression in parenchymal cells throughout the body triggered by endotoxin or by humoral factors i.e. IL-1, TNF- alfa, and IL-6 [30,31].

PCT concentrations increase more rapidly than CRP levels in patients with SBI. PCT levels begin to increase at two hours from the onset of infection and reach a serum peak at 24 to 36 hours [32]. For this reason, PCT has been shown to be a superior biomarker as compared with CRP for detecting SBI in ED [33]. However, the specificity for detecting SBI is limited, especially between infant < 3 months [25,34].

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Table 1. Kinetics of C reactive protein (CRP) versus procalcitonin (PCT) from the onset of inflammation.

Biomarker	Start of serum increase	Serum peak
CRP	4-6 hours	36-50 hours
PCT	2 hours	24-36 hours

In a consistent meta-analysis England et al. showed that serum PCT concentrations <0.3 ng/mL identify a population of febrile infants < 91 days of age at low risk for SBI [35]. They concluded that serum PCT concentration alone is anyway poorer predictor of SBI and may be used in combination with clinical valuation.

A meta-analysis to investigate the diagnostic accuracy of PCT as early biomarker of sepsis was performed including 1408 patients (1086 neonates and 322 children) [36]. In neonatal group PCT showed sensitivity of 85% (95% CI, 76% to 90%) and specificity of 54% (95% CI, 38% to 70%) at the PCT cut-off of 2.0-2.5 ng/mL. In the pediatric group it was not possible to undertake a pooled analysis at the PCT cut-off of 2.0-2.5 ng/ml, due to the paucity of the studies [36]. In a recent prospective multi-centre cohort study Waterfield et al. revealed no difference and only a moderate accuracy for PCT and CRP in detection of SBI in the ED reporting that the area under the curve was identical at 0.70 [37].

The diagnostic power of PCT in pediatric intensive care unit (PICU) is uncertain. PCT showed to adequately predict SBI in a heterogeneous PICU population, with a PCT of ≥1.28 ng/mL as the ideal threshold for detection of SBI as reported in a recent a retrospective cohort study [38]. Another retrospective study performed in PICU identified PCT value of ≥1 ng/mL as able to predict SBI with sensitivity of 70% and specificity of 68% [39]. In a retrospective observational study involving 646 critically ill children, Lautz et al. have found that peak blood PCT measured within 48 hours of PICU admission was not superior to CRP in differentiating SBI from viral illness and sterile inflammation, raising doubts about right timing to perform PCT in PICU [40]. Zeng et al. in a recent retrospective analysis found that PCT alone wasn't better be able to diagnose the hyperinflammatory state than CRP in PICU [41]. Furthermore, when both biomarkers are simultaneously elevated the diagnostic specificity of SBI increased.

3.3. Cytokines and chemokines

After infecting pathogens are recognized by toll-like receptors, host immune response is initiated mainly by the release of proinflammatory cytokines from macrophages and monocytes [25]. Because of this early involvement in the host immune response to infections, cytokines and chemokines have been considered as promising biomarkers of SBI, especially in recent years when most problems of their detection in blood samples have been solved. Moreover, as CRP and PCT production depends on cytokine release, it was thought that the measure of cytokines could offer an earlier and more effective evaluation of sepsis development compared to the traditionally used biomarkers [25]. Unfortunately, not all the expected benefits have materialized.

3.3.1. Interleukines (IL)

IL-2 is indicated as the most specific biomarker in patients with SBI, with low sensitivity and moderate specificity (54% and 86%, respectively) [42]. However, the poor predictive accuracy of this molecule doesn't outperform the discrimination of traditional sepsis biomarkers in the clinical practice.

IL-6 has been studied for its role in systemic inflammation. It is described as an acute phase pro-inflammatory cytokine, which increases its blood level within the first 6 hours, earlier than CRP, during bacterial infections [43]. It turns out to be useful in predicting SBI diagnosis in children with

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fever without apparent source [44]. In a large prospective study, even if blood level of IL-6 was higher in septic children, the difference between septic and non-septic group was not statistically significant [45]. Comparing blood draws collected at different arrival times, the sensitiveness decreases as the hours pass from the onset of the fever. Although pediatric data are few, evidence on the role of IL-6 in neonates with sepsis is promising [46,47]. IL-6 appeared as an early marker of neonatal sepsis, even if its levels tend to normalize during the development of infection, increasing false-negative findings [48,49].

The key role of increasing levels of IL-10 in anti-inflammatory response deals its relationship with worse outcomes in oncologic neutropenic patients with sepsis [50]. In recent findings, IL-10 appeared with high specificity and moderate sensitivity. While IL-6 decreases quickly in the first 12 ore from the onset of the blood infection, IL-10 tends to persist for longer during the septic state and performs as a valuable diagnostic biomarker [50].

However, many authors declared the superiority of combinations of blood biomarkers over individual tests in differential diagnosis of infection etiology [51,52]. It has been described that combination of WBC, ANC, CRP, IL-2 and IL-6 increase sensitivity to 96%, specificity of 81%, and a large AUC 0.942 (CI 95%, 0.859 to 0984) in differentiate bacterial pathogenesis [41]. Similarly, matching CRP with IL-10 levels, the clinician got a higher discriminative ability in etiology of infection (specificity from 77% to 98%, sensitivity 75%) [53].

Finally, recent preliminary studies have shown promising results on the specificity of IL-27 in early prediction of SBI in critical pediatric patients. Using a large genome-wide expression database of critical children in pediatric ED, predictors genes coding for IL-27 protein were described; in particular, EB13, a subunit of IL-27, appeared to have a high predictive role for bacterial infections (more than 90%) [54]. In comparison to PCT, IL-27 performed better in discriminating bacterial from viral infections. These findings, although preliminary, lead to consider IL-27 as an effective biomarker in bacterial sepsis, exhibiting a specificity of 95% in detection of infection. A CART-generated algorithm including IL-27, PCT and immune status led to an undisputed improvement in predictive value, statistically improved from either IL-27 or PCT alone [55].

3.3.2. TRAIL and IP-10

Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) is a type II transmembrane protein belonging to the TNF superfamily, which is involved in infection control and in the regulation of both innate and adaptive immune responses [56]. TRAIL is involved in sepsis by inducing apoptosis of inflammatory cells and down-regulating inflammation [57]. Many authors had explored the association between soluble TRAIL (sTRAIL) levels in septic patients and the risk of mortality: low sTRAIL levels seem to be associated with a high risk of mortality, with survivor patients who had significantly higher levels of sTRAIL than non-survivors [58].

IP-10 (i.e. interferon-gamma-inducible protein 10) is a chemokine that is expressed by antigen-presenting cells in response to IFN-γ and attracts activated T-cells to foci of inflammation [59]. This biomarker plays a role in the response to bacterial infections in particular in diagnosis and management of urinary tract infections, tuberculosis, and inflammatory diseases such as Kawasaki disease [60–62]

Van Houten et al. found that an assay combining three biomarkers, i.e. TRAIL, IP-10 and CRP, it is possible to distinguish bacterial from viral infections in febrile children with a sensitivity of 86.7% and a specificity of 91.1% [63]. In a proteomics-based study focusing on the host immune response, Oved and al. demonstrated that the combination of these three biomarkers showed a better performance compared to different combinations of routine biomarkers of inflammation in patients suffering from infectious diseases or from fever with unknown disease [64]. Papan et al. in a multinational, prospective, cohort study, validated the diagnostic performance of the novel host-response-based signature comprising TRAIL, IP-10, and CRP in a broad cohort of pediatric patients with respiratory tract infection or fever without source, demonstrating its capability to support diagnosis of viral etiology and reducing prescription of antibiotics [65]. Figure 1 shows how the novel host-response-based signature comprising TRAIL, IP-10, and CRP works.

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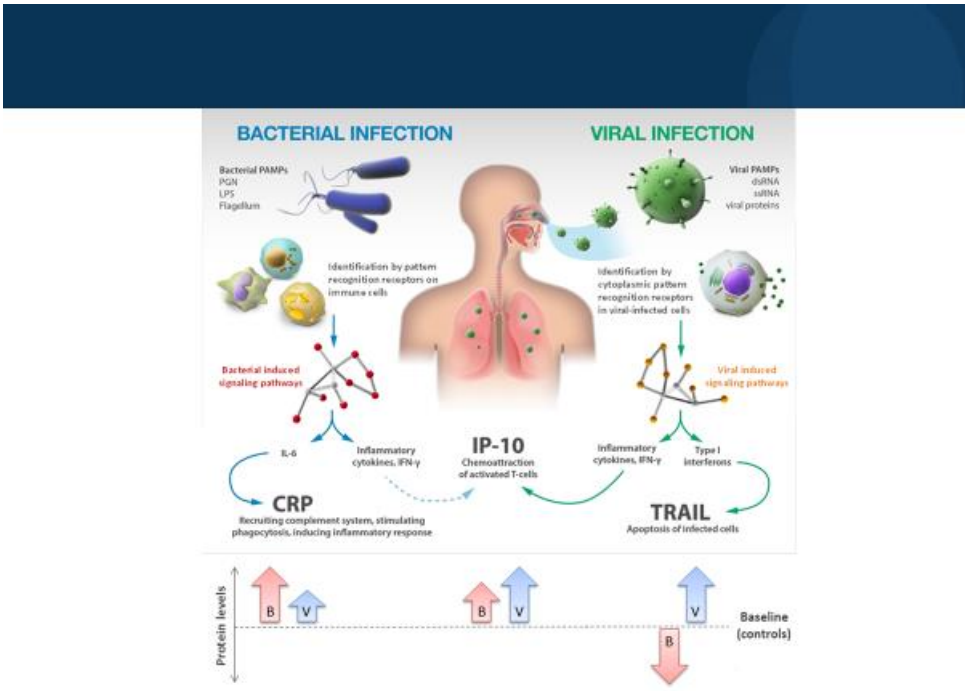

Figure 1. Novel host-immune signature for distinguishing between bacterial and viral infections.

4. Cell adhesion molecules

Several cell adhesion molecules including presepsin, cluster differentiation molecule-64 (CD64), soluble trigger receptor expressed on myeloid cell-1 (sTREM1), and pentraxin3 were tentatively used to differentiate septic children from non-septic ones [66]. However, only presepsin and sTREM1 were used in a number of studies useful for drawing some conclusion regarding their role in this regard.

4.1. Presepsin

Presepsin (sCD14-ST) is a protein related to cleavage of CD14, a soluble form of lipopolysaccharide (LPS) receptor, which recognizes pathogen-associated molecular patterns (PAMPs) and triggers the innate immune response [67]. This explains its specific elevation in bacterial infections, in which the underlying pathogenetic mechanism is expressed through the action of LPS.

Presepsin seems to have good specificity and sensitivity in sepsis and correlates to in-hospital mortality in patients with sepsis and septic shock, with a diagnostic potential that can increase if it is combined with clinical scores [68]. During the bacterial infectious state, the concentration in absolute value increases within 2 hours. Different studies reported that presepsin is the only biomarker that if remains elevated in patient with a SBI, it could be associated to higher risk of mortality throughout the follow-up period [69]. However, despite literature supporting its potential role in ED and in intensive care setting, some studies don't indicate a superiority of presepsin compared to other biomarkers in terms of sensitivity and specificity [70].

In neonatal sepsis, presepsin offers the advantage of identifying culture-negative sepsis, with the possibility of early initiation of antibiotic therapy [71]. Meanwhile, presepsin excludes the diagnosis of sepsis in newborns not likely to be affected, reducing the misuse of antibiotics, minimizing hospital stays, and avoiding selection pressure for resistant strains [72]. Levels of presepsin are significantly higher in neonates with sepsis than in healthy ones and they increased earlier than PCT or CRP; the rise in blood values of CRP and PCT is similarly high during early phase of infection, but presepsin alone decreases with antibiotic treatment [73,74].

The use in clinical practice of a combination model including presepsin in addition to CRP and PCT may be useful for early detection of SBI in children with fever admitted to ED and for monitoring response to therapy.

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4.2. STREM-2

Previous literature data show that sTREM-1 could be used as a marker of severity and outcome in septic neonates [75,76], while its diagnostic potential in pediatric patients older than one month seems to be moderate [78]. Systematic reviews and meta-analysis have recently evaluated the potential role of sTREM as a support in SBI diagnosis. However, low sensitivity and moderate specificity for sTREM-1 in distinguishing bacterial or viral etiology of infections were reported [78,79].

5. Future perspective

In pediatric patients, SBI is defined as the presence of systemic inflammatory response syndrome (SIRS) during evidence of an infection based on pathogen identification in the bloodstream or by the presence of symptoms directly linked to a high probability of systemic bacterial infection [80]. Early recognition of sepsis in children based on these definitions is often problematic, since blood cultures often provide false negative results and clinical symptoms are very unspecific, so emergencial setting management results in a delay of an adequate antimicrobial administration [81,82].

It is nowadays clear that combination of several SBI biomarkers instead of using one of the at the time can improve accuracy in SBI identification by unifying them into one diagnostic model/algorithm, as seen in adult patients [83]. Researchers also agree on the fact that crossing sepsis biomarkers with clinical and epidemiological information further optimizes accuracy. A retrospective cohort study aimed to evaluate the performance of a 2-step decision support algorithm based on an electronic health record best-practice alert (BPA) with age-adjusted vital sign ranges and physician screen [84]. The BPAs rely on presence of clinical markers of possible infection and incorporate patient risk factors, using demographic data, prior surgeries, or the patient's problem list and/or medication list, to recognize three different types of SBI risk stratified by the severity of the patient's underlying disease, with results that seem less specific in adults compared with children [85].

A German group has tried to develop and validate a diagnostic model for the discrimination of pediatric SBI and non-infectious SIRS, which could be set as an algorithm immediately ready for clinical practice [86]. Starting from a secondary analysis of a randomized controlled trial, they created a model including four clinical (length of PICU stay until onset of non-infectious SIRS/SBI, central line, core temperature, number of non-infectious SIRS/SBI episodes prior to diagnosis) and four laboratory parameters (interleukin-6, platelet count, procalcitonin, CRP), through a data driven analysis approach. Authors stated that the model could potentially reduce antibiotic treatment by 30% in non-infectious SIRS, emphasizing the importance of combining biomarkers and clinical parameters [86].

On this matter, there have been advances in the use of data-driven techniques to improve recognition of early signs of SBI: prediction models have been studied to obtain with machine learning a class of mathematical methods that attempt to generate knowledge and insight from large datasets [87]. Machine learning techniques has been shown useful also for the evaluation of inflammatory sub-phenotypes based on measurements of panels of inflammatory mediators either alone or in conjunction with clinical variables.

Considering both routine variables and inflammatory biomarkers in patients affected by acute respiratory distress syndrome (ARDS), a common complication of SBI, two sub-phenotypes have been consistently identified: hyper-inflammatory sub-phenotype with features such as higher levels of IL-6, IL-8, sTNFR1, higher rates of vasopressor use and lower circulating protein C and bicarbonate than a second hypo- inflammatory sub-phenotype [88]. The two phenotypes have been related to different responses to several therapies and highlighted bicarbonate, IL-6, IL-8, CRP, sTNFR-1 and vasopressor biomarkers as the most predictive variables for ventilator-free days and organ failure-free days.

Regarding septic shock therapy, another randomised trial highlighted data obtained from machine learning that has shown the IFNγ/IL10 ratio to be a good biomarker for the decision to administer hydrocortisone in septic shock [64]. Antibiotic administration and its optimization in

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critical ill children have also been studied as a field for potential algorithms implementation [89,90]. In a recent study it has been analysed the impact of a biomarker-based algorithm on broad-spectrum antibiotic prescribing in children with new-onset SIRS without proven bacterial infections admitted in a PICU [89]. This algorithm stated that PICU physicians should consider stopping antibiotics if: sterile site cultures obtained at SIRS onset revealed no growth after 48 hours, onset CRP and PCT were low and there was no sign of infection at exam or imaging. The authors noted a reduction of excessive broad-spectrum antibiotic therapy after algorithm implementation in patients in which a bacterial infection had been found, while no differences were seen in the so called uninfected patients except for the ones who had low biomarkers at the onset [89]. While de-escalation of antibiotic therapy in critically ill children remains a controversial topic, algorithms might ease the decision for patients with low biomarkers.

6. Conclusions

Inflammatory response is a complex mechanism in which many biochemical and immunological factors contribute to host response in SBI. Perfecting biomarkers accuracy could be useful for antimicrobial stewardship, pointing to more appropriateness in antibiotic prescription and dosage (Figure 2).

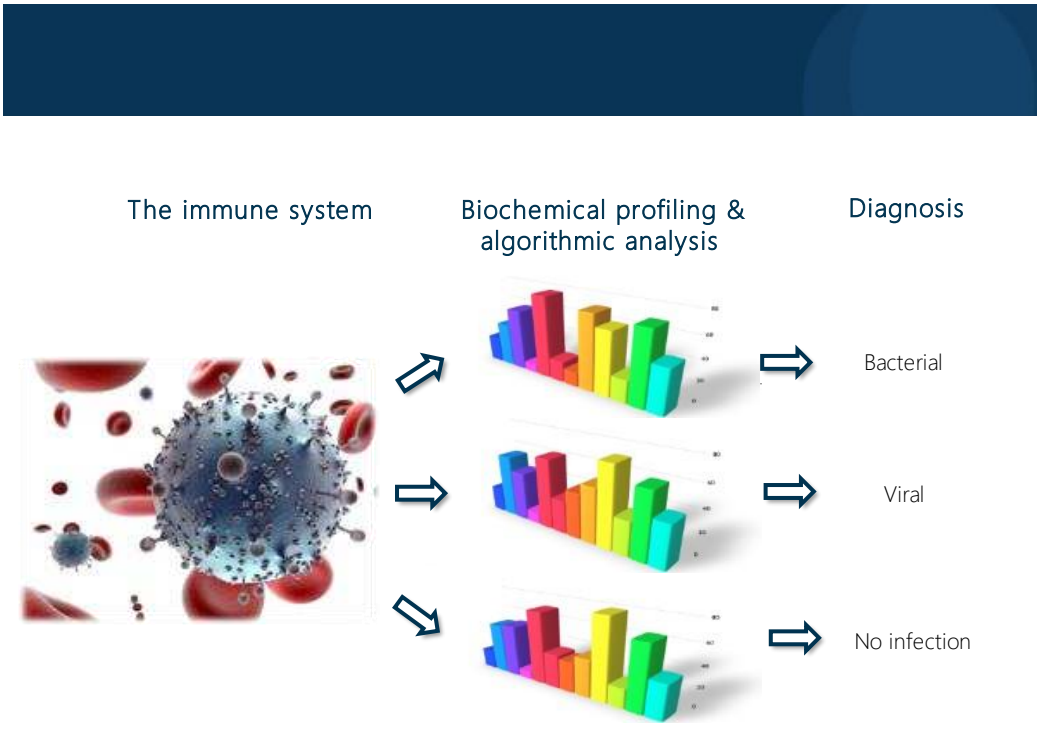

Figure 2. Decoding the body's immune system in order to detect the infection cause.

CRP and procalcitonin still represent the most used biomarkers in the pediatric ED for the diagnosis of SBI. Their sensibility and sensitivity increase when combined and for this reason it is reasonable to take them both into consideration in the evaluation of a febrile children. The potential of machine learning tools, who represent a real novelty in medical practice, in conjunction with routine clinical and biological information, may improve accuracy of diagnosis and target therapeutic options in SBI. However, studies on this matter are not yet validated in younger populations, making their relevance in pediatric precision medicine still uncertain. More data from further studies are necessary to improve clinical practice and decision making using these new technologies.

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