Biomarkers of infection and its complications in the critically ill

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Chapter 1

General introduction

Sandra H Hoeboer
GENERAL INTRODUCTION

Part I - Infections in the critically ill
Microbial infections, and associated complications, are still an important cause of intensive care (ICU) admissions and mortality.\(^1\) Despite the use of antibiotics and guidelines for supportive care mortality rates are up to 50% depending on disease severity.\(^1\)\(^-\)\(^7\) The most widely accepted definitions for infection are those of the “International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit” (ISFCC).\(^8\) According to ISFCC criteria the likelihood of infection is based mainly on clinical suspicion and/or microbiological cultures.\(^8\)

In clinical practice new onset fever, leukocytosis, tachypnea, tachycardia and elevated C-reactive protein (CRP) levels raise suspicion about the presence of infectious disease.\(^9\)\(^-\)\(^11\) They are, however, markers of host inflammation and their value for the definite diagnosis of infection has considerable limitations, especially in the ICU.\(^10\)\(^,\)\(^12\)\(^,\)\(^13\) The combination of fever, leukocytosis, tachypnea and tachycardia is considered the systemic inflammatory response syndrome to infection (SIRS). An infection in the presence of SIRS is called sepsis (Table 1). The adverse sequelae of infection: sepsis, septic shock, and organ failure, are partly caused by this host inflammatory response and each negatively influences outcome.\(^4\)\(^,\)\(^7\)\(^,\)\(^10\)\(^-\)\(^16\) In fear of undertreatment physicians repeatedly order cultures and start broad spectrum, empiric antibiotic treatment.\(^17\) However, overtreatment unnecessarily exposes patients to the risk of adverse drug reactions, amongst other risks. Prolonged antibiotic therapy also results in bacterial selection in individual patients and microbial resistance on a population level.\(^18\)\(^,\)\(^19\)

The methods currently used for microbiological confirmation of infection have considerable limitations. The reporting of microbiological results takes at least 1 or 2 days after collection of specimen and they are falsely negative in a third of patients suspected of infection.\(^6\)\(^,\)\(^9\)\(^,\)\(^16\) Cultures can also be falsely positive due to contaminants and may be insensitive in patients already treated with antibiotics.\(^20\) These limitations reduce the potential of microbiological cultures to monitor the response to antibiotic treatment.

To support the early diagnosis of infection, to predict its prognosis, and to monitor response to treatment a wide variety of inflammatory biomarkers have been studied.\(^21\) Nevertheless, controversy regarding the use of biomarkers for the diagnosis and prognosis of infections in the ICU remains.\(^21\) This could be the result of heterogeneous study populations and endpoints. Another explanation is that these biomarkers have been used to diagnose sepsis, the unspecific host inflammatory response to infection, and less often to diagnose microbiologically proven infection.
Part II - The Acute Respiratory Distress Syndrome

Severe infections and the host inflammatory response have an effect on individual organ systems as well. Around 75% of septic patients in the ICU develop respiratory failure requiring mechanical ventilation, while the lung is the primary site of infection in about 40-60% of cases.\(^1\)\(^-\)\(^4\),\(^6\),\(^14\),\(^16\) About half of the patients with sepsis fulfill the acute respiratory distress syndrome (ARDS) criteria.\(^1\),\(^4\),\(^14\),\(^16\) Mortality rates in ARDS patients vary between 20-50%, depending on disease severity.\(^22\),\(^23\) ARDS is caused by an insult to the alveolocapillary membrane that results in alveolocapillary inflammation and permeability that leads to formation of pulmonary oedema.\(^22\),\(^24\),\(^25\) There can be a direct insult to the alveolocapillary membrane such as pneumonia or an indirect insult due to the host inflammatory response. Infections are the main cause of ARDS.\(^22\),\(^24\)-\(^26\) The main symptom of ARDS is hypoxemia resulting from the generalised pulmonary oedema and reduced lung compliance.\(^22\),\(^27\),\(^28\) Besides the laborious, invasive, direct measurement of

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**Table 1. Definitions and criteria for the diagnosis of SIRS, sepsis and septic shock.**\(^7\)

**Systemic inflammatory response syndrome (SIRS)**

The clinical syndrome that results from a deregulated inflammatory response or to a non-infectious insult. The presence of at least 2 criteria are required for the diagnosis:

- Hyperthermia >38.3°C or Hypothermia <36°C
- Tachycardia >90 bpm
- Tachypnea >20 bpm
- Leukocytosis (>12 *10^9/L) or Leukopenia (<4 *10^9/L) or >10% bands.

**Sepsis**

SIRS secondary to clinically diagnosed infection. Positive cultures add to the validity but are not required for the diagnosis.

**Severe Sepsis**

Sepsis and at least one sign of hypoperfusion or organ dysfunction not explained by another known aetiology of organ dysfunction:

- Hypotension (SBP <90 mmHg or MAP <65 mmHg)
- Lactate >2 mmol/L
- Areas of mottled skin or capillary refill >3 seconds
- Creatinine >2.0 mg/dl
- Disseminated intravascular coagulation (DIC)
- Platelet count <100 *10^9/L
- Acute renal failure or urine output <0.5 ml/kg/hr for >2 hours
- Hepatic dysfunction as evidenced by Bilirubin >2 or INR >1.5
- Cardiac dysfunction
- Acute lung injury or ARDS

**Septic Shock**

Severe sepsis associated with hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <60 mmHg) despite adequate fluid resuscitation and/or a serum lactate level >4.0 mmol/L.
alveolocapillary permeability there is no true reference standard for diagnosis and monitoring ARDS at the bedside. To diagnose ARDS various clinical scoring systems have been developed. The recently developed Berlin definition (Table 2) is currently the preferred diagnostic standard in research, but controversy regarding its diagnostic value remains. A limitation of the Berlin definition is its dependency on ventilator settings. The level of positive end-expiratory pressure (PEEP) affects the oxygenation ratio and chest radiograph in mechanically ventilated patients. Moreover, the Berlin definition lacks a specific index of severity such as lung compliance. In contrast, the more extensive lung injury score (LIS, Table 2) gradually includes PEEP and lung compliance. Finally, chest radiographs, an important feature of both systems, are subject to considerable

<table>
<thead>
<tr>
<th>Table 2. Clinical classification systems of ARDS.</th>
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<tbody>
<tr>
<td><strong>Berlin definition of ARDS.</strong>&lt;sup&gt;23&lt;/sup&gt;</td>
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<tr>
<td><strong>Preconditions</strong></td>
</tr>
<tr>
<td><strong>Timing</strong></td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
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<tr>
<td><strong>Origin of oedema</strong></td>
</tr>
<tr>
<td><strong>Oxygenation</strong></td>
</tr>
<tr>
<td>Berlin 1: Mild ARDS: 200 &lt; (P_{a}O_{2}/F_{i}O_{2}) mmHg ≤300 with PEEP or CPAP ≥5 cmH(_{2})O</td>
</tr>
<tr>
<td>Berlin 2: Moderate ARDS: 100 &lt; (P_{a}O_{2}/F_{i}O_{2}) mm Hg ≤200 with PEEP ≥5 cmH(_{2})O</td>
</tr>
<tr>
<td>Berlin 3: Severe ARDS: (P_{a}O_{2}/F_{i}O_{2}) ≤100 mmHg with PEEP ≥5 cmH(_{2})O</td>
</tr>
<tr>
<td><strong>Lung injury score.</strong>&lt;sup&gt;29&lt;/sup&gt;</td>
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<tr>
<td><strong>Anterior-posterior chest radiograph score</strong></td>
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<tr>
<td>0= no alveolar consolidations</td>
</tr>
<tr>
<td>1= alveolar consolidations in 1 quadrant</td>
</tr>
<tr>
<td>2= alveolar consolidations in 2 quadrants</td>
</tr>
<tr>
<td>3= alveolar consolidations in 3 quadrants</td>
</tr>
<tr>
<td>4= alveolar consolidations in all quadrants</td>
</tr>
<tr>
<td><strong>PEEP score (when ventilated)</strong></td>
</tr>
<tr>
<td>0= PEEP ≤5 cmH(_{2})O</td>
</tr>
<tr>
<td>1= PEEP 6-8 cmH(_{2})O</td>
</tr>
<tr>
<td>2= PEEP 9-11 cmH(_{2})O</td>
</tr>
<tr>
<td>3= PEEP 12-14 cmH(_{2})O</td>
</tr>
<tr>
<td>4= PEEP &gt;15 cmH(_{2})O</td>
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</table>

The final lung injury score is obtained by calculating the average of all four categories.

No lung injury ≤1  mild ARDS 1-2.5  severe ARDS >2.5

Abbreviations: ARDS- acute respiratory distress syndrome, \(P_{a}O_{2}/F_{i}O_{2}\) - arterial \(O_{2}\) pressure over inspiratory \(O_{2}\) fraction, PEEP- positive end-expiratory pressure; pulmonary compliance=(tidal volume/(peak inspiratory pressure-PEEP).
interobserver variability. The correlation between both clinical diagnostic systems and diffuse alveolar damage on autopsy is limited. Particularly when occurring late in the intensive care unit (ICU) clinicians may underdiagnose ARDS and may be poorly able to quantify its severity and course, since clinical classification systems are not commonly used in daily practice. Availability of biomarkers that are associated with the severity and course of ARDS in the critically ill could simplify diagnosis, monitoring and therefore management of the syndrome in daily clinical practice.

**Biomarkers**

Ideally, a biomarker is an objective indicator of a physiologic or pathologic process that can be used for diagnosis, prognosis of disease and/or monitoring of response to treatment. In recent years much effort has been invested into research on biomarkers of infection and organ failure. The biomarkers under evaluation in this thesis represent markers of inflammation, circulatory homeostasis and endothelial barrier function (Table 3). Whether these biomarkers are useful for the monitoring of infections and organ failure is not known or still under debate.

**Aim and outline of the thesis**

**Part I** - We hypothesised that the increase in circulating inflammatory biomarkers during ICU-acquired infections depends on invasiveness and severity of disease. Therefore, the first goal is to find a single biomarker for discriminating between patients with and without microbial infection and to discriminate between those at low or high risk of developing infectious complications (i.e. bacteraemia, septic shock, death). The second is to determine its optimal cutoff value for biomarker-guided diagnostics and therapy in clinical practice and for future studies. We study the diagnostic accuracy and optimal cutoff of these biomarkers in 101 critically ill patients with new onset fever (chapter 2), 45 patients after elective esophagectomy (chapter 3), and perform a systematic review and meta-analysis of the literature on patients suspected of infection or sepsis (chapter 4). In addition, we hypothesised that the one-week course of biomarkers can be used to distinguish resolving microbial infection with a beneficial outcome from non-resolving or developing infections with a detrimental outcome associated with bacteraemia, septic shock, organ failure and death. In chapter 5 we try to define values at which antibiotic treatment can be decided as appropriate and might allow safe discontinuation in 72 critically ill patients one-week after new onset fever.

**Part II** - We aim to determine the association of routine biochemical variables (chapter 6) and potentially more specific biomarkers (chapter 7) with the severity and one-week course of late onset ARDS in 101 at risk critically ill patients after new onset fever. We hypothesised that biomarkers directly associated with inflammation (CRP, ANG2; PCT, IL6) or vasculary leakage (ANG2, albumin) would be more accurate than those indirectly
associated with inflammation (PTX3) or vascular/circulatory homeostasis (proADM), independent of underlying ARDS risk factor.

**Table 3.** Biomarkers studied in this thesis.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>C-reactive protein (CRP)</td>
<td>CRP is released from the liver in response to stimulation by IL6. It can bind to molecules on dead or dying cells and certain bacteria. It promotes phagocytosis by macrophages.</td>
</tr>
<tr>
<td>Procalcitonin (PCT)</td>
<td>PCT is released from all parenchymal cells after direct stimulation of endotoxins or indirectly through inflammatory mediators. Its biological function is unclear. PCT may discriminate between infectious and non-infectious inflammation and possibly between infections of bacterial and viral origin.</td>
</tr>
<tr>
<td>Interleukin 6 (IL6)</td>
<td>IL6 is a cytokine with pro- and anti-inflammatory properties. Released early in the inflammatory cascade it is a mediator of fever, the acute phase response, and production of neutrophils. IL6 can be elevated in many non-infectious inflammatory states as well.</td>
</tr>
<tr>
<td>Midregional pro-Ardenomedullin (proADM)</td>
<td>ProADM is the precursor hormone of ADM. ADM release is stimulated by a variety of hormones, cytokines, and physical stress. ADM is a strong vasodilator that maintains blood flow to individual organs. On top of that, ADM regulates and modulates complement activity, is bactericidal and has metabolic properties.</td>
</tr>
<tr>
<td>Midregional pro-Atrial Natriuretic Peptide (proANP)</td>
<td>ProANP is the precursor hormone of ANP. ANP has well known natriuretic, kaliuretic, diuretic, vasodilative effects but also less known immune modulating properties. ANP is secreted as a resultant of atrial stretch mainly, but also by stimulation of pro-inflammatory cytokines. The reduced ejecction fraction, increased ventricular diastolic volume and pressure observed in severe sepsis may explain the increase in ANP levels.</td>
</tr>
<tr>
<td>Copeptin</td>
<td>Copeptin is the precursor hormone of arginin vasopressin (AVP). AVP is important for maintaining circulatory homeostasis by regulating fluid balance and vascular tone in response to osmotic and hemodynamic stimuli. Increased levels are reported in the early phase of septic shock, while a relative AVP deficiency is seen in patients late during septic shock.</td>
</tr>
<tr>
<td>Angiopoietin-2 (ANG2)</td>
<td>ANG2 is released from the weibel palade bodies of endothelial cells after direct or indirect stimuli. Angiopoietin-2 dysregulates the endothelial barrier function in almost all organs promoting interstitial oedema and inflammation.</td>
</tr>
<tr>
<td>Pentraxin-3 (PTX3)</td>
<td>PTX3, is produced primarily in endothelial cells, macrophages and dendritic cells in response to stimulation by IL1 and Tumor Necrosis Factor-α, but not IL6. PTX3 has a role in inflammation and innate immunity.</td>
</tr>
<tr>
<td>Albumin</td>
<td>An important molecule to maintain plasma colloid oncotic pressure that can behave as a negative acute phase protein. In disease states with increased vascular permeability the extravasation of albumin and the resultant low plasma colloid oncotic pressure promotes the formation of oedema.</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>LDH is present in most cells but its physiologic levels are low. During cell injury large amounts of LDH can be released systemically.</td>
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REFERENCES


