Strategies to optimise the treatment of community-acquired pneumonia

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CHAPTER 1

General introduction, aim and outline of the thesis

COMMUNITY-ACQUIRED PNEUMONIA

Pneumonia is an infection of the alveoli of the lungs, which is clinically characterised by a pulmonary infiltrate on chest radiograph accompanied by symptoms such as cough, fever, sputum production and dyspnoea.[1] Pneumonia can be divided into three types based on place of acquirement: hospital-acquired pneumonia, ventilator-acquired pneumonia and community-acquired pneumonia (CAP).[2] This thesis will only focus on CAP, pneumonia acquired outside the hospital. In the Netherlands, CAP is most frequently caused by *Streptococcus pneumonia* followed by *Haemophilus influenza* and atypical bacteria. Viruses such as Influenza virus, are responsible for 3-5% of hospitalised CAP cases and approximately one third of viral pneumonia is also accompanied by bacterial pneumonia.[3–5] In the period in which the studies presented in this thesis were performed, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) emerged as a new pathogen for CAP and led to the COVID-19 pandemic. Therefore, this thesis will distinguish between two types of CAP: non-COVID-19 pneumonia (from here on referred to as CAP) and hospitalised COVID-19 (from here on referred to as COVID-19). Both will be discussed, though CAP is the main focus of this thesis.

Globally pneumonia is among the leading causes of death due to infectious diseases.[6] The incidence of CAP is highest in young children and the elderly. In the Netherlands, there were 156.000 new cases of CAP in 2020. In that same year 24.205 patients were hospitalised with CAP and 2.726 patients died due to CAP. The annual health care costs for CAP are substantial, in the Netherlands the healthcare cost for CAP was estimated at 584 million euros in 2019 of which 61,3% was allocated to hospital care.[7] Identifying strategies to optimise the management of CAP might aid in lightening the burden of CAP.

The cornerstones of CAP treatment are early diagnosis and swift initiation of appropriate empiric antimicrobial treatment, preferably within 4 hours of hospital presentation.[8] Empiric antimicrobial treatment is based on the most likely causative organism and disease severity.[9] Empiric antimicrobial treatment should be switched to targeted treatment once the causative pathogen is identified. Appropriate antimicrobial therapy is essential in the treatment of CAP as it improves clinical outcomes and reduces the selective pressure for antimicrobial resistance.[10–12] Yet, in some patients appropriate antibiotic therapy is not enough to prevent unfavourable clinical outcomes. An excessive or dysregulated host immune response can lead to severe disease accompanied by lung injury, sepsis and eventually multi-organ damage and death.[13,14] This has led to an interest in immunomodulation in CAP. In COVID-19 a similar mechanism is thought to play a role: dysregulation of the host immune response triggered by SARS-COV-2 is thought to cause inflammatory organ injury resulting in unfavourable clinical outcomes.[15]

ADJUNCTIVE CORTICOSTEROID TREATMENT IN CAP

The host inflammatory response in CAP is a complex interaction between the numerous cells and soluble mediators of the immune system. The response is regulated by cytokines and chemokines, the messengers of the immune system. Cytokines are produced by multiple cell types (e.g., neutrophils, macrophages, epithelial cells). They recruit, regulate and activate immune cells such as neutrophils and initiate local repair processes. The interaction between pro-inflammatory cytokines and anti-inflammatory cytokines determines the nature, duration and intensity of the host immune response.[16] Corticosteroids are potent non-specific inhibitors of the immune system. Corticosteroids have multiple anti-inflammatory mechanisms. The most important being the deactivation of genes that encode for pro-inflammatory cytokines (e.g., IL-6 and IL-8) and the activation genes that encode for anti-inflammatory cytokines (e.g., IL-10).[17,18] In CAP, corticosteroids have shown to downregulate the cytokine response.[19] Furthermore, corticosteroids inhibit the migration of neutrophils to the site of infection.[20] It is hypothesised that downregulation of the host immune response by corticosteroids can reduce pulmonary damage and inhibit the development of sepsis ultimately reducing unfavourable clinical outcomes.[21]

The first well-designed randomised clinical trial investigating adjunctive corticosteroid treatment in CAP was published in 2005 by Confalonieri et al.[22] The study was terminated after the first interim analysis (n = 46) due to far better improvement of the PaO2/FiO2 ratio and a lower mortality rate (0% vs 30%) in the intervention group. Several large trials have followed most with positive albeit less spectacular results.[23–27] An individual patient data meta-analysis (IPDMA) including 6 trials showed that corticosteroids reduced length of hospital stay (LOS) by 1 day and improved time to clinical stability (TTCS). Yet, corticosteroids did not reduce mortality in CAP.[28] This begs the question if a 1-day LOS reduction outweighs the possible adverse event of corticosteroid use. This dilemma is further complicated by the fact that, in the IPDMA, CAP-related rehospitalisation was more frequent in patients treated with corticosteroids compared to placebo (5.0% vs 2.7%).[28] Currently treatment guidelines for CAP do not advise the routine use of adjunctive corticosteroid treatment.[9]

Nonetheless, it has been hypothesised that corticosteroids could be more effective in patients with severe disease as patients with severe disease show a more exuberant immune response.[29,30] Hence, a subgroup of CAP patients may exist for whom the benefits of corticosteroid treatment outweigh the risks. The IPDMA suggested a possible greater effect of corticosteroids on LOS in patients with severe disease based on pneumonia severity index (PSI) score.[28,31] No RCT has prospectively tested this hypothesis. Therefore **Chapter 2** aims to prospectively investigate whether the effect of adjunctive corticosteroid treatment depends on disease severity. In this randomised placebo-controlled trial (the Santeon-CAP study) randomisation is stratified by disease

severity based on PSI risk class. The Santeon-CAP study is the sequel to the Ovidius trial by Meijvis et al.[24] in which 6 mg dexamethasone reduced LOS by 1 day. In the Ovidius trial dexamethasone was administered intravenously. It was hypothesised that this may have hampered iv-to-oral switch of antibiotics thereby delaying discharge. Therefore, in the Santeon-CAP study, oral dexamethasone is investigated.

INFLAMMATORY SUBGROUPS FOR GUIDING CORTICOSTEROID TREATMENT IN CAP

As mentioned above, it is thought that corticosteroids are most effective in patients with more severe disease based on the rationale that severe disease is caused by higher levels of inflammation. In **Chapter 2**, PSI score is used to define subgroups. However, the PSI score is a mortality risk score and is greatly influenced by age.[31] Consequently, the PSI score does not necessarily correspond to level of inflammation. Parameters more indicative of inflammation may be more appropriate to identify patients in whom corticosteroid treatment is more effective. Yet identification of such a parameter has proven a challenge; Analysis of parameters such as C-reactive protein, ICU admission, or systemic inflammatory response criteria, have not resulted in the identification of a well-defined CAP subgroup benefitting more from corticosteroid treatment.[28] Therefore, besides PSI score, this thesis explores two additional methods for identifying CAP subgroups which might benefit more from corticosteroid treatment.

The first method is based on white blood cell (WBC) count differential parameters. WBCs are important effectors in the local and systemic inflammatory response in CAP.[32] Neutrophilia is widely used as a marker of inflammation in CAP. More recently, lymphocytopenia has been associated with disease severity and higher concentrations of inflammatory cytokines in CAP.[33] Furthermore, the neutrophil-lymphocyte count ratio (NLR) has been acknowledged as a marker of systemic inflammation.[34–36] In CAP, NLR has been associated with disease severity and has shown to predict mortality.[37,38] **Chapter 3** examines whether these parameters could also be used to guide corticosteroid treatment. In **Chapter 3** a post-hoc analysis of the Santeon-CAP study is performed to test whether the effect of adjunctive oral dexamethasone on clinical outcomes is modified by a high neutrophil count, low lymphocyte count and/or high NLR.

The second method used in this thesis to identify CAP subgroups is latent class analysis (LCA) of inflammatory and clinical parameters. LCA is a statistical modelling method used to identify “hidden" subgroups in a population by identifying individuals that share similar characteristics. Unlike other outcome modelling approaches LCA recognises the fact that some clinical factors can share variance as a constellation of observed variables for a common unobserved (latent) variable.[39] LCA uses this relationship between observed variables to group individuals together into mutually exclusive and collectively exhaustive subgroups. The subgroups identified by LCA are

called 'latent classes'. In general, LCA subgroups are solely based on baseline data or patient characteristics and thus are not dependent on an outcome variable. LCA is useful in defining the unobservable heterogeneity in a population.[39,40]

In acute respiratory distress syndrome LCA has successfully identified subgroups with different inflammatory profiles. These clinically distinct subgroups were shown to respond differently to ventilator and fluid management.[41,42] In COVID-19 related ARDS LCA also identified two clinically distinct subgroups. Both subgroups responded differently to corticosteroid treatment. Corticosteroids improved mortality in the hyperinflammatory subgroup but worsened mortality in the hypoinflammatory subgroup.[43] **Chapter 4** and **Chapter 5** examine whether LCA can also identify clinically distinct subgroups in CAP and if so, whether these subgroups respond differently to adjunctive corticosteroids. Therefore, in **Chapter 4** and **Chapter 5**, LCAs of baseline clinical and biomarker data collected at time of hospital admission are performed in three independent CAP cohorts.

DEXAMETHASONE FOR COVID-19

As discussed above adjunctive corticosteroids for CAP have been a subject of research for many years and no definitive conclusions have been made regarding its place in the treatment of CAP. In COVID-19 this is quite different. Dexamethasone has been studied as a stand-alone treatment for COVID-19. Trials studying corticosteroids for COVID-19 were commenced promptly after the Sars-CoV-2 virus emerged. The rationale for corticosteroids being that severe COVID-19 (defined as an oxygen saturation <94%), is caused by a dysregulated host immune response in reaction to the SARS-CoV-2 virus.[15] Just several months after COVID-19 was declared a pandemic the preliminary results from RECOVERY Trial and the results of the WHO react meta-analysis were published. The results showed that 6 mg dexamethasone reduced risk for mortality and mechanical ventilation.[44,45] The choice to investigate a 6 mg dose was partially based on the dose used in the Ovidius trial.[24] After publication of these studies, dexamethasone 6 mg for 10 days became standard treatment for hospitalised COVID-19 patients requiring oxygen therapy.[46,47]

Trials investigating corticosteroids for COVID-19 did not perform subgroup analyses based on BMI despite the fact that obesity had been associated with ICU admission and mortality.[48,49] Because dexamethasone is a lipophilic drug with a relatively large volume of distribution, one may hypothesise that serum dexamethasone levels are lower in patients with obesity compared to those with normal weight which might translate in the fixed 6 mg dexamethasone dose being less effective in patients with overweight or obesity.[50–52] To test this hypothesis, **Chapter 6** examines whether overweight and obesity are associated with worse clinical outcomes in a cohort of non-ICU COVID-19 patients treated with fixed-dose dexamethasone.

MICROBIOLOGICAL TESTING AND ANTIBIOTIC ALTERATIONS IN CAP

Though immunomodulation might improve outcomes for CAP patients, as mentioned earlier, appropriate antibiotic treatment is still the basis of CAP treatment. A quality indicator of appropriate antimicrobial treatment is the adjustment of the empirical antibiotic regimen guided by microbiological test results.[53] Yet to do so, the availability of actionable microbiological test results is necessary. In >60% of CAP cases a causative micro-organism is not identified.[9] Microbiological diagnostics consist of traditional cultures of blood and respiratory samples, newer techniques such as PCR assays on throat and nose swabs for identifying atypical bacteria and respiratory viruses, and urinary antigen tests for legionella and pneumococcus. In a research setting, the combination of traditional and newer tests had the potential to increase the percentage of identified pathogens up to 67%.[54–56] However, there is little evidence if the same is true in day-to-day clinical practice and more importantly, whether extensive testing leads to more alterations of the empirical antimicrobial regimen in individual patients. Therefore, **Chapter 7** examines whether extensive microbiological testing is associated with an increase in diagnostic yield and antibiotic treatment alterations in day-to-day clinical practice.

AIMS OF THE THESIS

The aim of this thesis was to identify strategies to improve the management of community-acquired pneumonia outside the intensive care unit with a focus on corticosteroid treatment. This thesis specifically focuses on the following three topics:

1. The effect of oral adjunctive dexamethasone on clinical outcomes in CAP and whether CAP subgroups exist in which the benefits of adjunctive corticosteroids outweigh the disadvantages of corticosteroid use.

2. The association between obesity and overweight and clinical outcomes in COVID-19 patients treated with dexamethasone.

3. The relationship between the extent of microbiological testing and early alterations of antibiotic therapy in CAP.

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