Strategies to optimise the treatment of community-acquired pneumonia

Wittermans, E.

CHAPTER 8

Summary, general discussion and future perspectives

SUMMARY

The aim of this thesis was to identify strategies to optimise the treatment of hospitalised community-acquired pneumonia patients (CAP) outside an intensive care unit (ICU) setting with a focus on corticosteroid treatment. First, this thesis focused on the question whether oral adjunctive corticosteroid treatment improves outcomes in hospitalised CAP patients and tries to identify a subgroup of CAP patients, based on inflammatory status at admission, in whom the beneficial effects of adjunctive corticosteroid treatment outweigh the disadvantages associated with corticosteroid use. Different methods were used to define subgroups. Next, this thesis investigated whether obesity and overweight were associated with worse clinical outcomes in a population of hospitalised COVID-19 patients who were all treated with the recommended fixed 6 mg dexamethasone dose. The aim was to test the hypothesis that 6 mg would be less effective in patients with obesity compared to patient with normal weight due to the pharmacokinetic properties of dexamethasone. Last, this thesis focused on optimising antibiotic treatment by exploring whether extensive microbiological testing facilitates early antibiotic alterations in CAP patients.

Chapter 2 describes the results of the multicentre placebo-controlled randomised Santeon-CAP trial. In this trial non-ICU patients with CAP were randomised to receive a 4-day course of 6 mg oral dexamethasone or placebo within 24 hours of hospital admission. Randomisation was stratified by disease severity (PSI risk class I-III vs class IV-V). Dexamethasone reduced median length of stay (LOS) by 0.5 days (5.0 vs 4.5 days; p =0.033) and reduced ICU admission rate (3% vs 7%; p = 0.03). Mortality rates did not differ between intervention and placebo group. Within both disease severity subgroups dexamethasone did not significantly reduce LOS. In the mild-moderate disease subgroup dexamethasone reduced ICU admission rate, the same was not found in the severe pneumonia group. Though not statistically significant, the rate of hospital readmission tended to be twice as high in the dexamethasone group compared to the placebo group.

In **Chapter 3** a post hoc-analysis of the Santeon-CAP study was performed in which white blood cell (WBC) differential parameters were used to define CAP subgroups. It was observed that in patients with a high WBC count (≥ 15.6 10^9 cells/l), high neutrophil count (≥ 13.2 10^9 cells/l) and high neutrophil-to-lymphocyte ratio (≥ 15.5) dexamethasone reduced LOS by 2 days, while there was no effect of dexamethasone on LOS in patients with a lower WBC count, lower neutrophil count or lower NLR ratio. White blood cell differential parameters did not modify the effect of dexamethasone on ICU admission or mortality.

In **Chapter 4** latent class analysis (LCA), a statistical method to identify 'hidden' subgroups in a population, was used to define subgroups using multiple inflammatory and clinical parameters. LCA was performed in two independent CAP cohorts: A Swiss cohort with patients from a multicentre trial investigating adjunctive prednisone

treatment (STEP trial), and a Dutch cohort with patients from a prospective observational study (Triple-P study) and a multicentre trial investigating adjunctive dexamethasone treatment (Ovidius trial). In both cohorts LCA identified two clinically distinct subgroups. One subgroup with more excessive inflammation and worse prognosis (class 2) and one subgroup with less exuberant inflammation and a better prognosis (class 1). In patients who participated in the Ovidius trial, the effect of corticosteroids on LOS was greater in Class 2 compared to Class 1. The same was not observed in the STEP trial.

Chapter 5 aimed to validate the findings described in **Chapter 4** in a third independent CAP cohort. Therefore, the LCA was repeated in the Santeon-CAP cohort. The LCA model used for the Ovidius-TripleP cohort was replicated as closely as possible. Again, LCA was able to identify the same two clinically distinct subgroups as in **Chapter 4**. Thus, proving LCA identified subgroups robustly. Yet the finding of a greater effect of dexamethasone in class 2 compared to class 1 patients could not be replicated.

Chapter 6 examined whether overweight and obesity are associated with worse clinical outcomes in COVID-19 patients treated with fixed-dose dexamethasone. In a population of patients admitted with COVID-19 to the general ward and treated with dexamethasone according to protocol (6 mg dexamethasone daily for 10 days of until discharge), overweight and obesity were not associated with worse clinical outcomes.

Chapter 7 explores the relationship between the extent of microbiological testing and early antibiotic treatment alterations in hospitalised CAP patients. There was a stepwise increase in the percentage of patients with altered antibiotic regimens by day three of hospitalisation for each additional type of microbiological test performed. A PCR assay for atypical pathogens was most strongly associated with antibiotic treatment alterations.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The aim of the studies presented in this thesis was to identify strategies to optimise the treatment of patients hospitalised with community-acquired pneumonia with a focus on corticosteroids. In this general discussion the implications of the studies presented in this thesis will be discussed and perspectives for future research will be provided.

ADJUNCTIVE CORTICOSTEROID TREATMENT FOR CAP

Adjunctive corticosteroid treatment in CAP has been a much researched and debated topic. The rationale being that corticosteroids attenuate the systemic inflammatory response and could thereby prevent an unfavourable clinical course caused by an excessive or dysregulated immune response.[1] A considerable number of studies have investigated whether adjunctive corticosteroid treatment improves outcomes for hospitalised CAP patients.[2–9]

Positive effects of adjunctive corticosteroid treatment in CAP

Interpreting the results of adjunctive corticosteroid trials is somewhat of a challenge as trials differ greatly in patient population and intervention (e.g., corticosteroid type, dose and treatment duration). An individual patient data meta-analysis (IPDMA) of six corticosteroid in CAP trials showed that adjunctive corticosteroid treatment reduced length of hospital stay (LOS) by 1.0 day and reduced time to clinical stability. However, corticosteroids did not reduce ICU admission or 30-day mortality rates.[10] A meta-analysis by Stern et al. did find a mortality benefit of adjunctive corticosteroid treatment in patients with severe CAP, yet this was based on the results of a small single-centre, single blinded study in which criteria for disease severity were not reported. Furthermore, re-analysis of the baseline characteristics of that study showed that kidney function was significantly worse in the control group compared to the intervention group at randomisation.[8,11,12] Table 1 provides an overview of the characteristics and results of the studies included in the IPDMA[10], the Santeon-CAP study (**Chapter 2**) and the most recent corticosteroid trial by Meduri et al.[13]

Most corticosteroid studies investigated intravenous corticosteroid treatment. In **Chapter 2** (The Santeon-CAP study), the effect of oral corticosteroid treatment was studied in a non-ICU population. This study showed that 4 days of 6 mg oral dexamethasone reduced LOS by 0.5 days. In addition, dexamethasone also reduced the risk of ICU admission after initial admission to a general ward. The Swiss STEP trial is the only other study that has investigated adjunctive treatment with oral corticosteroids (prednisone 50 mg). This study also showed that adjunctive corticosteroid treatment reduced LOS but it did not find a beneficial effect of prednisone on ICU admission or mortality.[3]

Table 1 Overview of characteristics and results of corticosteroid trials

Study	Country	No	Population	Intervention	Primary outcome	Median LOS (Corticosteroid vs placebo)	ICU admission* (Corticosteroid vs placebo)	Mortality (Corticosteroid vs placebo)
Confalonieri (2005)	Italy	46	Severe CAP (ATS criteria)	Hydrocortisone 200mg iv bolus followed by 10mg/h iv for 7d	Improvement PaO2/FiO2#	21 vs 13†	N/A	38% vs 0%† (60d)
Snijders (2010)	The Netherlands	204	Hospitalised CAP	Prednisone 40mg iv or po for 7d	Clinical cure day 7	10.0 vs 10.6§	N/A	5.8% vs 5.5% (30d)
Meijvis (2011)	The Netherlands	302	Hospitalised CAP (non-ICU)	Dexamethasone 6mg iv for 4d	LOS#	6.5 vs 7.5†	5% vs 7%	6% vs 7% (30d)
Fernandez-Serrano (2011)	Spain	52	Severe CAP (consolidation of ≥2 lobes and PO_2/FIO_2<300)	mPRED 200 mg iv bolus followed by tapering (3.3–0.8 mg/h) over 9 d	Respiratory failure requiring MV or NPPV	10 vs 12	17% vs 23%	4% vs 5% (>9d)
Blum (2015)	Switzerland	785	Hospitalised CAP	Prednisone 50mg po for 7d	Time to clinical stability#	6.0 vs. 7.0†	4% vs 6%	4% vs 3% (30d)
Torres (2015)	Spain	120	Severe CAP (ATS or PSI criteria and CRP >150 mg/L)	mPRED 0.5 mg/kg iv twice daily for 5d	Treatment failure#	11 vs 10.5	0% vs 0%	10% vs 15% (In hospital)
Briel (2018)‡	-	1506			All-cause 30d mortality	7.0 vs 8.0†	5.6% vs 6.3%	5.0% vs 5.9% (30d)
Wittermans (2021)	The Netherlands	401	Hospitalised CAP (non-ICU)	Dexamethasone 6mg po for 4d	LOS#	4.5 vs 5.0†	3% vs 7%†	2% vs 4% (30d)
Meduri (2022)	United States	584	Severe CAP (ATS criteria or ICU or intermediate care unit admission).	mPRED 40mg/day 7 days followed by tapering over 20d	60d all-cause mortality	7 vs 8	N/A	16% vs 18% (60d)

*Intensive care unit admission after initial admission to a general ward.
†Statistically significant difference between treatment groups.
§LOS reported as mean
‡Individual data meta-analysis of the studies by Confalonieri, Snijders, Meijvis, Blum, Fernandez-Serrano and Torres.
#Statistically significant difference between intervention and placebo group for the primary outcome
Abbreviations: d days; ATS American Thoracic society; PSI pneumonia severity index; ICU intensive care unit; mPRED Methylprednisolone; LOS length of hospital stay; MV mechanical ventilation; NPPV non-invasive positive pressure ventilation

From these findings, one can conclude that both iv and oral adjunctive corticosteroid treatment reduce LOS in hospitalised CAP patients. Yet, a reduction in LOS is the only benefit of adjunctive corticosteroids that has consistently been reported across multiple studies. Because results regarding ICU admission and mortality are conflicting, the effect of corticosteroids on ICU admission and mortality remains uncertain. Furthermore, over the years both LOS and mortality rate have decreased for hospitalised CAP patients (Table 1). For example, in the Ovidius trial[2] (2011) which had a similar population to that of the Santeon-CAP study, median LOS in the control group was 7,5 days compared to 5 days in the control group of the Santeon-CAP study. This means that, assuming a constant relative effect, the absolute effect of corticosteroids will become smaller compared to the time in which the first large corticosteroid trials were conducted. In studies showing that corticosteroids reduce LOS, LOS was reduced by approximately 10%. In earlier trials this translated into a 1-day reduction in LOS whereas in the Santeon-CAP study, the most recent trial, this translated into a 0.5-day reduction. The important question is whether the beneficial effect of adjunctive corticosteroid treatment on LOS outweighs the risks of corticosteroid treatment.

Adverse effects of adjunctive corticosteroid treatment in CAP

Because corticosteroids stimulate the gluconeogenesis, hyperglycaemia is a common side effect of corticosteroid treatment. Not surprisingly, hyperglycaemia is the most reported adverse effect of corticosteroid therapy in CAP trials.[10] In **Chapter 2**, the observed risk of hyperglycaemia was higher in patients treated with dexamethasone compared to placebo (7% vs 1%; p =0.001).

Another concern is a possible increased risk of hospital readmission in patients treated with corticosteroids. This concern was first raised in the IPDMA by Briel et al., where a higher percentage of CAP-related readmissions was observed in patients treated with corticosteroids compared to those treated with placebo (5.0% vs 2.7%).[10] In **Chapter 2**, readmission rate was twice as high in the dexamethasone group compared to the placebo group (5% vs 10%, p = 0.051). Even though differences between intervention and placebo group were not statistically significant in **Chapter 2**, it does further complicate the question if a 10% reduction in LOS is enough to justify adjunctive corticosteroid treatment for CAP patients. The above suggests that adjunctive corticosteroids should not be routinely prescribed in all hospitalised CAP patients, which is in line with the current recommendations in national and international guidelines.[14,15]

CAN CAP SUBGROUPS BE DEFINED IN WHICH THE BENEFICIAL EFFECTS OF ADJUNCTIVE CORTICOSTEROID TREATMENT OUTWEIGH THE RISKS?

High serum levels of inflammatory mediators, which are indicative of a high systemic inflammatory response, are associated with disease severity in CAP.[16–21] It has been hypothesised that corticosteroids might be beneficial in patients with severe CAP with an excessive immune response, but not in patients with non-severe CAP and a low or well-balanced immune response.[22] Yet, identifying clinical and/or laboratory parameters that can distinguish between these groups upon hospital admission has proven a challenge. Several options will be discussed below.

Disease severity based on clinical prediction scores

The Santeon-CAP study (**Chapter 2**) was the first trial specifically designed to assess whether the effect of adjunctive corticosteroids differs between patients with mild-moderate CAP (PSI I-III) and severe CAP (PSI IV-V).[23] Randomisation was therefore stratified by disease severity at time of hospital admission. There was no statistically significant difference in effect of dexamethasone between both groups, though the effect of dexamethasone on LOS seemed greater in the patients with mild-moderate pneumonia compared to those with severe pneumonia. However, due to the early termination of the trial combined with a shorter LOS and lower mortality rate than expected, there might not have been enough statistical power to show a difference between treatment arms within the disease severity subgroups. The IPDMA also assessed whether the effect of corticosteroids differed according to PSI score. Contrary to the results in the Santeon-CAP study, the IPDMA suggested that the effect of corticosteroids might be greater in patients with severe CAP compared to those with mild-moderate CAP, yet the effect did not differ significantly between groups.[10] These results indicate that the PSI score does not adequately distinguish between patients who do and patients who do not benefit from corticosteroid treatment. This might be due to the fact that the PSI score does not necessarily correspond to level of inflammation.

The PSI score is a predictor for mortality, it is therefore heavily influenced by age and comorbidities[23]; clinical signs and symptoms of excessive inflammation or severe disease contribute less to the PSI score. Other clinical scores for identifying patients with severe disease are the American Thoracic Society (ATS) criteria and the CURB-65 (acronym for confusion, urea, blood pressure and >65 years of age). These scores rely more on clinical criteria than on age and co-morbidities and thus might be more appropriate to identify patients with severe disease based on inflammation.[15,24] In a sensitivity analysis of the Santeon-CAP study (**Chapter 2**) in patients aged ≤65, the largest reduction in LOS was observed in patients with a high CURB-65 score. Further prospective research is necessary to confirm these results.

C-reactive protein

C-reactive protein (CRP) is a readily available inflammatory biomarker which is widely used in day-to-day clinical practice. In a trial investigating adjunctive methylprednisolone, Torres et al. only included ICU patients with a CRP >150mg/L. They observed less treatment failure in the intervention group compared to the control group.[5] **Chapter 2** also showed a shorter LOS and lower rate of ICU admission in patients with a CRP above the median (≥210 mg/L) who were treated with dexamethasone compared to those who received placebo. However, the IPDMA subgroup analyses based on CRP did not show a differential treatment effect of corticosteroids on LOS or mortality between patients with a CRP above the median (≥188 mg/L) and those with a CRP below the median.[10] An issue with CRP is that it has slower kinetics compared to other inflammatory biomarkers. Mendez et al. showed that serum CRP concentrations were dependent on days since symptom onset. Patients who presented to hospital within 3 days of symptom onset had lower levels CRP concentrations than patients presenting after 3 days, while procalcitonin, interleukin-6 (IL-6) and interleukin-8 (IL-8) were already elevated.[25]

White blood cell count differential parameters

Neutrophil-to-lymphocyte ratio (NLR) and lymphocyte count are easily obtainable parameters upon hospital admission. Both have been associated with level of inflammation and clinical outcomes in CAP.[26,27] In **Chapter 3** a greater effect of dexamethasone was observed in patients with higher peripheral neutrophil counts and a higher NLR. In patients with a WBC count ≥ 15.6 10^9 cells/l, a neutrophil count ≥ 13.2 10^9 cells/l and NLR ≥ 15.5 dexamethasone reduced LOS by 2 days, while there was no effect of dexamethasone on LOS in patients with a lower WBC count, lower neutrophil count or lower NLR. In all white blood cell differential parameter subgroups, both high and low, the percentage of hospital readmission was higher in patients treated with dexamethasone compared to those who received a placebo. For the high WBC count, neutrophil count and NLR subgroups a 2-day decrease in LOS should be weighed against a possible higher risk of hospital admission.

No other studies have assessed for effect modification by WBC differential parameter subgroups on the effect of corticosteroids on clinical outcomes in CAP. A recent study in COVID-19 patients found that patients with a NLR > 6.11 had a greater effect of low dose corticosteroids than patients with a NLR <6.11.[28] Though COVID-19 is a different disease than CAP.

Because there was no effect modification by lymphocyte count in **Chapter 3**, the greater effect of dexamethasone in patients with a high NLR was presumably driven by a high neutrophil count rather than by a low lymphocyte count. Ebrahimi et al. showed that CAP is associated with pronounced neutrophil extracellular trap (NET) formation.[29] Furthermore, the authors found that NETosis was modulated by prednisone and that the effect of adjunctive prednisone treatment on time to clinical stability was

modified by NET marker levels. The authors hypothesised that the beneficial effects of corticosteroid treatment in CAP may be due to modulation of NET formation or neutrophil pre-activation. Neutrophil function was not assessed in **Chapter 3**, though this hypothesis may explain why the effect of dexamethasone was modified by neutrophil count. This is further supported by the fact that higher peripheral neutrophil counts were associated with higher levels of NET markers in the study by Ebrahimi et al. It would be interesting to further elucidate the effects of corticosteroids on neutrophil function in CAP. A better understanding might aid in the identification of patients who would benefit from corticosteroid treatment.

For now, neutrophil count or NLR might be promising parameters for guiding corticosteroid treatment in CAP. Specifically because a leukogram is cheap, easy to perform and in many cases is routinely performed as part of the initial patient work-up. Yet, the results of **Chapter 3** should be interpreted with caution due to its retrospective nature and it being a single centre study. The findings need to be validated in a separate CAP cohort after which prospective validation would be necessary.

Multiple systemic inflammatory biomarkers

The above focuses on single, readily available parameters as predictor for corticosteroid response in CAP (clinical prediction scores, WBC differential counts, CRP). Yet the inflammatory response in CAP is a complex interaction between numerous mediators. Furthermore, not one but several clinical parameters are associated with systemic inflammation. Thus, there are numerous laboratory and clinical parameters that determine inflammation. Therefore, combining multiple parameters that are indicative of systemic inflammation might be a more appropriate approach to identify a CAP subgroup more likely to benefit from corticosteroid treatment. Latent class analysis (LCA) is a statistical method that uses multiple patient characteristics to identify 'hidden subgroups' in a population (**Chapter 1** provides a brief description of LCA). In acute respiratory distress syndrome LCA has successfully identified two clinically distinct subgroups, a hypoinflammatory and hyperinflammatory subgroup, both requiring different strategies for fluid and ventilator management.[30,31] **Chapter 4** and **Chapter 5** explored whether LCA could also identify clinically distinct subgroups in CAP and if so, whether these subgroups respond differently to adjunctive corticosteroids.

In **Chapter 4** and **Chapter 5**, LCAs of baseline inflammatory and clinical parameters were performed in three independent cohorts of CAP patients. In **Chapter 4** LCA was performed in two independent cohorts: the combined Ovidius-Triple P cohort and the Swiss Step cohort.[2,3,32] In both cohorts LCA identified a subgroup with more excessive systemic inflammation and worse prognosis (class 2), and a subgroup with less systemic inflammation and better prognosis (class 1). In Ovidius trial patients, a greater effect of adjunctive dexamethasone treatment on LOS in class 2 compared to class 1 was observed. The same was not found in the STEP cohort. **Chapter 5** aimed

to validate the finding from the Ovidius cohort in the Santeon-CAP cohort. Similar to the Ovidius-TripleP and STEP cohorts, two clinically distinct subgroups of CAP patients were identified. Yet, the finding of a larger effect of corticosteroids in Class 2 compared to class 1 could not be replicated despite a similar population and the use of the same dexamethasone dose as in the Ovidius trial. Taken together, LCA of baseline clinical and inflammatory parameters can identify clinically relevant CAP subgroups with different inflammatory profiles and different clinical outcomes. Yet, a differential effect of corticosteroids between classes was only found in one out of three analysed cohorts. Thus, LCA defined classes did not prove robust in the identification of patients in whom corticosteroids have a greater positive effect. It is important to note that the sample size of class 2 in the Santeon-CAP cohort (n=84) may have been too small to show differences between classes.

Besides a possible sample size issue, there are also other hypotheses that may explain why the response to corticosteroid only differed between classes in one out of three cohorts. First, unmeasured parameters such as the pulmonary inflammatory response might influence the corticosteroid response. The pulmonary inflammatory response and degree of pulmonary damage were not measured in **Chapter 4** and **Chapter 5** nor in other chapters in this thesis. Several studies have shown that the cytokine response is more intense in the lung than in serum and that for most cytokines the levels in serum and in bronchoalveolar lavage fluid are not correlated.[18,19,33] It is plausible that the nature or the extent of pulmonary inflammatory response or the degree of pulmonary damage in CAP may influence the response to corticosteroids.

Second, it has been shown that the inflammatory response in CAP can exhibit signs of concurrent hyperinflammation and immune suppression.[34] One could hypothesise that corticosteroids would not benefit patients with concurrent immune suppression. Third, it has been proposed that corticosteroid resistance might be the cause of the negative or conflicting findings in trials investigating corticosteroids for sepsis.[35] Last, it is possible that high concentrations of some inflammatory mediators contribute to pulmonary damage and sepsis whilst others are necessary for clearing infection. Because corticosteroids downregulate a broad range of inflammatory mediators, it is possible that they also downregulate vital parts of the inflammatory response.

ADJUNCTIVE CORTICOSTEROIDS FOR CAP: CONCLUSION AND FUTURE PERSPECTIVES

Based on the borderline significant results of the Santeon-CAP study and a general trend of decreasing LOS and mortality for CAP patients, the routine use of corticosteroids for all non-ICU patients hospitalised with CAP is not recommended. Due to a lack of a clearly defined and validated subgroup of CAP patients for whom the benefits of adjunctive corticosteroid treatment outweigh the risk, adjunctive corticosteroid treatment is also not recommended for a specific subgroup.

Corticosteroids might still be beneficial for a specific subgroup of patients for whom the benefits outweigh the risks. Yet, further research would be necessary to define and validate such a subgroup. In this thesis, LCA defined subgroups based on inflammatory parameters only modified corticosteroid response in one out of three cohorts. Though there may have been insufficient power to show a difference in corticosteroid effect in the 3rd cohort due to the relatively small number of patients in class 2. Analysis of a larger cohort would be necessary to definitively determine whether LCA of baseline clinical and inflammatory data can identify a subgroup of CAP patients for whom the beneficial effects of corticosteroids outweigh the risks. This thesis also showed that dexamethasone had a greater effect in patients with high peripheral neutrophil counts and a high NLR, but these results require validation. It would be interesting to further elucidate the role of corticosteroids on neutrophil function in CAP and see if this could lead to new insights in guiding corticosteroid therapy. Furthermore, the IPDMA by Briel et al.[10] is currently being updated. The updated IPDMA will include data from the Santeon-CAP study (**Chapter 2**) and the recently published corticosteroid in CAP trial by Meduri et al.[13] The addition of patients from two additional studies may increase statistical power sufficiently to identify CAP subgroups for which corticosteroid treatment is more effective.

DEXAMETHASONE FOR COVID-19

In **Chapter 6**, it was postulated that COVID-19 patients with overweight or obesity would benefit less from the fixed 6 mg dexamethasone dose compared to patients with normal weight. This was based on the assumption that systemic exposure of dexamethasone would be lower in patients with a higher BMI due to the lipophilic nature of dexamethasone. To test this hypothesis, the outcomes between patients with overweight and obesity were compared to those with normal weight in a population of hospitalised COVID-19 patients who were all treated with the recommended 6 mg dexamethasone dose. The results showed that overweight and obesity were not associated with an unfavourable clinical course in this population. Hence, the hypothesis could not be confirmed.

After the study described in **Chapter 6** was completed, a trial comparing the pharmacokinetics of 6 mg dexamethasone between COVID-19 patients with normal weight and COVID-19 patients with obesity was published by Abouir et al.[36] This trial confirmed that COVID-19 patients with obesity had lower serum concentrations of dexamethasone compared to patients with normal weight. This indicates that different dosing should be used in patients with obesity to achieve similar exposure to patients with normal weight. However, in agreement with the results in **Chapter 6**, this trial noted that despite lower serum dexamethasone concentrations in patients with obesity there was no difference in LOS or duration of ICU stay between patients with obesity and those with normal weight.

An explanation for why clinical outcomes were not worse for patients with overweight or obesity compared to those with normal weight despite lower systemic exposure to dexamethasone may be the finding in **Chapter 6** of a lower inflammatory state in patients with obesity compared to those with normal weight. Perhaps, the lower inflammatory state of patients with obesity indicates that lower serum peak dexamethasone concentrations are sufficient in patient with obesity compared to patients with normal weight as there is less inflammation to dampen.

Two randomised trials have compared high dose vs low dose dexamethasone in COVID-19; In the COVID steroid-2 study (6 mg vs 12 mg) days alive without life support and 28-day mortality did not differ significantly between study arms.[37] In the study by Taboada et al. higher dose dexamethasone (20 mg) decreased clinical worsening within 11 days (primary endpoint) but did not improve time to recovery, ICU admission or mortality.[38] Unfortunately, these trials did not report subgroup analyses based on BMI. To definitely answer the question whether outcomes for COVID-19 patients with overweight or obesity can be improved by using higher doses of dexamethasone subgroup analyses in prospective randomised trials are necessary. However, based on the fact that obesity was not associated with worse clinical outcomes in **Chapter 6** nor in the trial by Abouir et al., for now it seems unlikely that patients with obesity or overweight require a higher dexamethasone dose.

MICROBIOLOGICAL TESTING AND ANTIBIOTIC TREATMENT ALTERATIONS IN CAP

Chapters 2 through 5 aimed to optimise CAP treatment by adding corticosteroids to standard treatment with antibiotics. Yet, antimicrobial treatment remains the basis of the treatment of CAP. **Chapter 7** explored whether extensive microbiological testing could improve antibiotic treatment.

An important indicator of appropriate antimicrobial treatment is the alteration of empirical antibiotics based on microbiological test results.[39] In clinical practice, no causative micro-organism is identified in >60% of CAP patients, which can hamper appropriate adjustment of antibiotic treatment.[14] **Chapter 7** showed that, in day-to-day clinical practice, more extensive microbiological testing within the first 2 days of hospital admission was associated with a higher frequency of early antibiotic alterations. A PCR assay for atypical pathogens contributed most to antibiotic treatment alterations, the odds of antibiotic alteration were 2.6 times higher if a PCR assay for atypical pathogens was performed. The influence of PCR assays on antibiotic modification was less outspoken in a different Dutch study of patients with lower respiratory tract infections (not limited to CAP). Oosterheert et al. found that antibiotic treatment was only modified in 11% of patients based on PCR assays for atypical pathogens and respiratory viruses when these were added to the standard microbiological testing protocol.[40] This is most likely caused by the difference in proportion of patients receiving dual therapy (beta-lactam combined with an antibiotic to cover of atypical bacteria) at admission. The majority of alterations in **Chapter 7** were switches from dual- to monotherapy, both positive and negative PCR results provide opportunities for this alteration. In the study by Oosterheert et al. only 16% received dual therapy compared to 35% in **Chapter 7**, thus PCR assays would have less potential to alter treatment. The above illustrates that differences in local antimicrobial treatment protocols and patient population may lead to different results in different centres. Nonetheless, a general recommendation would be to at least perform a PCR assay for atypical pathogens in all patients for whom the empiric antibiotic regimen includes an antibiotic with the purpose of covering atypical bacteria.

CONCLUSIONS

This thesis discussed several strategies to improve the treatment for community-acquired pneumonia outside an ICU setting. It showed that more extensive microbiological testing facilitates early alteration of antibiotic treatment in CAP. A general recommendation would be to at least perform a PCR for atypical pathogens in patients treated with dual therapy upon admission.

Based on the results of the corticosteroid studies presented in this thesis and other available evidence, the routine prescription of adjunctive corticosteroids for all CAP patients is not recommended. Currently, the benefits of corticosteroid treatment do not seem to outweigh possible risks associated with corticosteroid use in CAP. This thesis could not identify a robust subgroup of CAP patients in whom the risk-benefit ratio is acceptable. Peripheral neutrophil counts or NLR seem promising parameters for possible guiding of corticosteroid therapy as the effect of dexamethasone on LOS was greater in patients with high neutrophil counts or a high NLR. Yet, validation of these findings is required. LCA could only identify a subgroup benefiting more from corticosteroid treatment in one out of three analysed cohorts. Because there may have been insufficient power to show a difference in corticosteroid effect in the third cohort, analysis of a larger cohort would be necessary to definitively determine whether LCA of baseline clinical and inflammatory data can identify a subgroup of CAP patients for whom the beneficial effects of corticosteroids outweigh the risks. Furthermore, regarding COVID-19, based on the currently available evidence patients with overweight or obesity do not require higher doses of dexamethasone compared to patients with normal weight.

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