PART III
CONCLUSIONS

CHAPTER 10

SUMMARY OF FINDINGS

Yuri van der Does MD

SUMMARY OF FINDINGS

Part I Procalcitonin-guided therapy

Chapter 2: In this systematic review, we report on prospective studies on PCT-guided antibiotic therapy. In the six studies on adult patients with respiratory complaints, PCT-guided therapy reduced antibiotic prescriptions. In three studies on pediatric populations, there was no reduction in antibiotics, due to nonadherence to the PCT-guided therapy protocol. PCT-guided therapy did not increase adverse events. Chapter 3: In this pilot study, we randomized 106 patients with fever in the ED between PCT-guided antibiotic therapy and standard care. There was no significant reduction in antibiotics in the PCT-guided group, although a trend was noted (92% vs 80% of patients received antibiotics). The PCT-guided group had significantly less ICU admissions and mortality. We concluded that the sample size was insufficient and hypothesized that effects could be shown in a sufficiently powered study. Chapter 4: The protocol of the HiTEMP study: Higher diagnostic accuracy and cost-effectiveness using procalcitonin in the treatment of emergency medicine patients with fever. Chapter 5: In the HiTEMP study, 551 patients were included. We found no significant reduction in antibiotics in the PCT-guided group (73% vs 77%, p = 0.28). PCT-guided therapy was noninferior by means of adverse events. The accuracy of PCT ≥0.5µg/L for confirmed bacterial infections was low, with a sensitivity 0.52(95% CI 0.45–0.60) and a specificity 0.74(95% CI 0.68–0.78). However, the accuracy for confirmed bacterial infections was higher for PCT than for CRP. The costs of treatment were equal between groups, € 5386 for patients in the control group, and € 4853 for patients in the PCT-guided group, with a mean difference of -€533(95% CI -€1570 to €505). Our hypothesis was that low accuracy of PCT for bacterial infections explained the lack of effect of PCT-guided therapy.

Part II Additional biomarker strategies

Chapter 6: In this pilot study of 54 patients with confirmed infections, we showed that the blood concentrations of biomarkers TRAIL and IP-10 were significantly higher in patients with viral disease compared to patients with non-viral disease (TRAIL: p <0.001) (IP-10: p = 0.05). A combined model of PCT, TRAIL and IP-10 resulted in an area under curve (AUC) of 0.84 (95% CI 0.72 – 0.97) for identifying confirmed viral disease. Chapter 7: In this study of 315 patients from the HiTEMP cohort, we used a combined biomarker model of CRP, PCT, TRAIL and IP-10 for the prediction of suspected and confirmed bacterial infections resulted in an AUC of 0.77 (95% CI 0.70 – 0.83). Chapter 8: In a study on disease severity on 353 patients of the HiTEMP cohort, we found that the biomarkers proADM, proET-1 and suPAR predicted ICU admission with similar accuracy as the clinical score SIRS and qSOFA, and predicted mortality with a higher accuracy than the clinical scores. CRP and PCT had limited predictive value for ICU admission, and predicted mortality to a lesser extent than

proADM, proET-1 and suPAR, but more accurate than SIRS and qSOFA.

Part III Conclusions

Chapter 9: In this last part, we summarize the findings of the studies in this thesis. PCT-guided therapy did not reduce antibiotics in a general population with fever in the ED. Combinations of biomarkers (CRP, PCT, TRAIL and IP-10) could discriminate between bacterial and non-bacterial disease with higher accuracy than individual markers. Biomarkers (CRP, PCT, proADM, proET-1 and suPAR) could identify patients who were at risk for a severe course of illness and mortality.

Furthermore, two new research projects are described. The first project will continue differentiating bacterial from non-bacterial disease using the combined biomarker model of CRP, PCT, TRAIL and IP-10 in the ED. The second project will further deepen the knowledge on severity of disease in patients with suspected infections in the acute and critical care setting. The future diagnostic modalities of systems biology are addressed, and future treatments, including bacteriophage therapy, are described.