FACULTY OF MEDICINE AND HEALTH SCIENCES

Antimicrobial stewardship in the intensive care unit: evolving challenges and data science opportunities

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The ongoing rise in antimicrobial resistance necessitates optimal usage of available antimicrobials, especially in high-stakes environments such as the intensive care unit (ICU). In this dissertation, we aimed to on the one hand seize a unique opportunity to evaluate the impact of an unprecedented worldwide pandemic on antimicrobial practices during the COVID-19 crisis. On the other hand, we set out to develop a machine-learning (ML) based clinical decision support system (CDSS) that aids in optimizing antimicrobial therapy in critically ill patients and to try to bring this CDSS bedside.

In chapters five and six, we report on some specific infection management characteristics during the 2020 and 2021 COVID-19 waves based on two large observational multicentric point prevalence studies. We found that antimicrobial use on admission was disproportionate considering the clinically diagnosed rate of bacterial co-infection, while we also noted an increase in the use of immunomodulatory therapies. The impact of rapidly evolving evidence at that time was clearly illustrated by a substantial rise in corticosteroid usage in 2021 vs 2020, although our observational data from 2020 denoted a correlation between corticosteroid use and the occurrence of ICU-acquired infections and infections with multidrug-resistant organisms.

In chapter seven, we commence the ML CDSS development journey by evaluating target attainment of pragmatically optimized dosing regimens of two commonly prescribed beta-lactam antimicrobials in the ICU: piperacillin and meropenem. In this monocentric prospective observational study, we found that despite utilizing such dosing regimens, a proportional percentage of patients did not attain plasma concentrations within the therapeutic range when a minimal inhibitory concentration multiplication of 2 or more needed to be targeted. This was especially the case for piperacillin. Furthermore, we illustrated that using a worst-case scenario rather than a pathogen-based scenario potentially skews the target attainment and efficacy analysis of research. Hence, for the evaluation of the relationship between target attainment and morbidity and mortality, we advocated for the use of a pathogen-based approach if possible.

Chapters eight and nine describe our efforts to develop ML models that can aid in optimizing piperacillin and meropenem dosing. In chapter eight, we provide a proof of concept by developing three ML models using a data-driven approach. The models predict the antimicrobial plasma concentration of piperacillin, while at the same time providing uncertainty quantification of their prediction. Our overall best-performing model was a CatBoost model, which performed equally well during external validation as a published PopPK model. In chapter nine, we divert from the data-driven approach and combine ML with pharmacometrics. We developed ML models that can predict the PK constant of piperacillin and meropenem and consequently can also give dosing advice. Although there was a performance drop when externally evaluating the models, their performance was still on par with clinical applicability standards.

To foster clinical adoption of our models, we utilized a mixed-methods approach to identify practical, psychological, behavioural, legal, and ethical preconditions posed by end-users to use an ML-based CDSS in clinical ICU practice. We present our findings of this study in chapter ten. The most important preconditions that were identified were explainability, seamless integration in the clinical workflow, and prospective clinical trials that prove patient safety and clinical impact. Trust was identified as a key precondition with both psychological and behavioural impact. In chapter eleven, we attempted to meet the explainability requirement by

developing a dashboard that incorporated several local explainability techniques. In a small test group of physicians, ceteris paribus profiles (which show the effect of a change in the variable on the output if all else remains stable) were identified as the most useful of the 'out-of-the-box' explainable AI (XAI) techniques that were evaluated. With an average score of 7 out of 10 for explainability, the responses from the practising physicians demonstrated the potential impact of an XAI dashboard on clinical decision-making.

In this dissertation, we made considerable progress towards developing a CDSS that aids in optimizing antimicrobial therapy in critically ill patients and bringing this CDSS bedside. While the original research illustrates the potential of AI/ML to bring us one step closer to high-quality personalized antimicrobial dosing for ICU patients, some of the remaining hurdles and caveats are acknowledged in chapter twelve (discussion) and chapter thirteen (future perspectives). Identifying the optimal PK/PD target for beta-lactam antimicrobials, overcoming the Achilles heel of data-driven ML prediction models, and bolstering trust and clinical adoption of ML models are important topics that will need to be addressed. Given the diverse research, practical, technical, legislative, and ethical aspects of these questions, multidisciplinary collaboration will be essential to bridge the gap between AI/ML research and clinical practice, as was illustrated throughout this dissertation.

Curriculum Vitae

Thomas De Corte graduated from Ghent University as an MD in 2016. He embarked on his PhD journey in 2020. He became an accredited internist in 2023 and is currently specializing in clinical haematology.

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