Individualized prognosis in childhood immune thrombocytopenia

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Part VI

APPENDIX

a

DEFINITIONS

- `Translational medicine` is medical research that is concerned with facilitating the practical application of scientific discoveries to the development and implementation of new ways to prevent, diagnose, and treat disease. (Merriam Webster) It is an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside, and community. (European Society for Translational Medicine; Wikipedia)
- `Personalized medicine` is a medical model that separates people into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease. The terms personalized medicine, precision medicine, stratified medicine and P4 medicine are used interchangeably to describe this concept. (Wikipedia)
- `Systems medicine` looks at the systems of the human body as part of an integrated whole, incorporating biochemical, physiological, and environment interactions. (Wikipedia)
- `Syndrome.` "A syndrome is a recognizable complex of symptoms and physical findings which indicate a specific condition for which a direct cause is not necessarily understood. Once medical science identifies a causative agent or process with a fairly high degree of certainty, physicians may then refer to the process as a disease, not a syndrome. (Calvo et al. AMIA Annu Symp Proc 2003; 802). "The advance of medical semantics is in general, towards causation (Pearce Pract Neural 2011; 11).

- `Etiology` is the cause of a disease. Compare pathogenesis, the origination and development of a disease.
- `Genetic susceptibility.` A susceptible individual is a member of a population who is at risk of contracting a disease. Genetic variation can, in some cases, result in disease, or in susceptibility to disease. (Modified from Wikipedia)
- `Confounding.` A confounder is a variable that influences both the dependent variable and independent variable, causing a spurious association. (Wikipedia)
- `Effect modification` occurs when an exposure has a different effect among different subgroups. Effect modification is associated with the outcome but not the exposure. (Students 4 Best Evidence). Statistically, this can be thought of as an interaction, which may arise when considering the relationship among three or more variables. An interaction and describes a situation in which the effect of one causal variable on an outcome depends on the state of a second causal variable. (Wikipedia)
- `Heterogeneous treatment effects.` The study of heterogeneity of treatment effect (HTE) is the study of these differences across subjects: For whom are there big effects? For whom are there small effects? For whom does treatment generate beneficial or adverse effects? Research on such questions can help inform theories about the conditions under which treatments are especially effective or ineffective. (Evidence in Governance and Politics) More formally, heterogeneity of treatment effect is the nonrandom, explainable variability in the direction and magnitude of treatment effects for individuals within a population. The main goals of HTE analysis are to estimate treatment effects in clinically relevant subgroups and to predict whether an individual might benefit from a treatment. (Agency for Healthcare Research and Quality)

- `Bias (statistics).` The bias of an estimator is the difference between an estimator's expected value and the true value of the parameter being estimated. Algorithms with high bias typically produce simpler models. High bias can cause an algorithm to miss the relevant relations between features and target outputs (underfitting). (Modified from Wikipedia)
- `Variance (statistics)` measures how far a set of numbers (e.g., an estimator) are spread out from their average value. Models with high variance are usually more complex. High variance can cause an algorithm to model the random noise in the training data, rather than the intended outputs (overfitting). (Modified from Wikipedia)
- `Bias-variance tradeoff.` Ideally, one wants to choose a model that both accurately captures the regularities in its training data (low variance), but also generalizes well to unseen data (low bias). It is typically impossible to do both simultaneously. Feature selection can decrease variance by simplifying models. Similarly, a larger training set tends to decrease variance. Adding features (predictors) tends to decrease bias, at the expense of introducing additional variance. Learning algorithms typically have some tunable parameters that control bias and variance. In linear and generalized linear models, regularization decreases model variance at the cost of increasing bias. (Modified from Wikipedia)
- `Dogmalysis.` Dogma is something held as an established opinion; a point of view or tenet put forth as authoritative without adequate grounds. Lysis is a process of disintegration or dissolution (as of cells). "Physicians need to experience the humility of having our ignorance exposed. This is necessary to keep medicine science-based." (Cliff Reid)
- `Bayesian probability` is an interpretation of the concept of probability, in which, instead of frequency or propensity of some phe-

nomenon, probability is interpreted as reasonable expectation representing a state of knowledge. To evaluate the probability of a hypothesis, the Bayesian probabilist specifies a prior probability. This, in turn, is then updated to a posterior probability in the light of new, relevant data. (Wikipedia)

b

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PHD PORTFOLIO

David Emanuel Schmidt, PhD period 2016 – 2022.
`Promotor:` Prof. Masja de Haas
`Co-promotor:` Dr. Marrie Bruin
`Co-promotor:` Dr. Gestur Vidarsson

COURSES

2017 Analysis of Repeated Measurements, LUMC

2017 Regression Analysis: Advanced Biostatistics, LUMC

2017 European Network of Immunology Institutes (ENII) Summer School

2017 Postgraduate Course Advanced Immunology, VUMC/Sanquin

FIXED MILESTONES

2018 Basis Course for Clinical Investigators (BROK)

Basic Methods and Reasoning in Biostatistics (Exemption)

2016 PhD Introductory Meeting

CONFERENCES

2019 American Society for Hematology (ASH), Orlando (Poster)

2019 International Society of Thrombosis and Hemostasis (ISTH), Melbourne (Oral)

2019 American Society for Hematology (ASH), San Diego (Poster)

2018 European Congress for Thrombosis and Hemostasis (ECTH), Marseille (Oral)

2018 Nordic Coagulation Meeting, Stockholm (Oral)

2018 European Congress for Immunology, Amsterdam

2018 European Society for Platelet and Granulocyte Immunology (ESPGI), Ede (Oral)

2017 American Society for Hematology (ASH), Atlanta, USA (Poster; not attended)

2017 International Society of Thrombosis and Hemostasis (ISTH), Berlin (Poster)

2016 European Society for Platelet and Granulocyte Immunology (ESPGI), Stockholm

SEMINARS

2019 Amsterdam Kindergeneeskunde Symposium

2018 Amsterdam Kindergeneeskunde Symposium

2017 PhD Retreat, Amsterdam Infection & Immunity Institute

2016 Blood Transfusion Support to Treat &Prevent Bleeding

SUPERVISION & TEACHING

2018 Master thesis, Anke Lakerveld (MSc Biology of Disease, Utrecht University).

2017 Bachelor thesis, Lisa Kok (HBO Laboratory Sciences, InHolland)

2016 Bachelor thesis, Ashwini Kanhailal (BSc Biomedical Sciences, Utrecht University)

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CURRICULUM VITAE

David Emanuel Schmidt, born 11 january 1989 in Bad-Nauheim (Germany), graduated from high school with Allgemeine Hochschulreife (Abitur; Albert-Einstein-Schule Gross Bieberau) in 2008 and enrolled in the BSc Biomedical Sciences program at Maastricht University in 2009. He graduated cum laude in 2012, including a two-year Honours Program in International Health. He was, amongst others, vice-chairman of the University Council and co-founder of the Gezondheidsuniversiteit. He stayed for a summer at the Institute of Public Health, Bangalore (India), and performed research internships in cellular hemostasis and vascular pathology during two years. He also obtained a scholarship from the German Academic Merit Foundation (Studienstiftung des Deutschen Volkes).

In 2012 he enrolled at Utrecht University for the Research Master MD/MSc Clinician Scientist Training Program (Selective Utrecht Medical Master, SUMMA), from which he graduated in 2016. During this time, he was chairman of the SUMMA student council and a project associate at Interstedelijk studenten overleg (ISO). He co-founded the Gezondheidscursus at Utrecht University Medical Center and the Royal Dutch Academic of Sciences (KNAW) Arts & Science program. He also co-founded the Right Research done for the Right Reasons (2RR) action program together with the European Organization for Nuclear Research (CERN), Royal Technical University (KTH) and Karolinska Institutet (Stockholm). He did research and clinical internships in hemostasis, intensive care and transfusion medicine at University Medical Center Hamburg-Eppendorf (UKE, 2013), Karolinska Institutet (Stockholm, 2014 and 2016), Wilhelmina Childrens Hospital Utrecht (2015), and McMaster University/Hamilton General Hos-

pital (Canada, 2016). He also contributed to research projects in vascular pathology and pediatric intensive care over two years.

In 2016, he started graduate studies (PhD candidate) at Sanquin Research-Landsteiner Laboratory, Amsterdam University Medical Center and Leiden University Medical Center Graduate School in a shared project with Wilhelmina Childrens Hospital, Utrecht. He obtained a PhD scholarship (Promotionsförderung) from the Studienstiftung des Deutschen Volkes and participated to the Training Upcoming Leaders In Pediatrics (TULIPS) postdoc curriculum. The research obtained awards, amongst others, from the International Society for Thrombosis and Hemostasis (ISTH), American Society of Hematology (ASH, San Diego and Orlando), European Congress for Thrombosis and Hemostasis (ECTH), and Nordic Coagulation Meeting (NordCoag).

Since 2020, he is working at the Pediatric Coagulation Unit and training as specialist in pediatrics at Astrid Lindgren Childrens Hospital (ALB), Karolinska University Hospital. He also works as postgraduate researcher at the Department of Womens and Child Health (KBH) and the Coagulation Unit at Karolinska Institutet. He is teaching evidence-based medicine methods for medical students in the hemostasis course (2020, 2021). Current research projects include improvements of diagnostic methods in hemostasis using whole genome sequencing for bleeding disorders, evaluation of assays for primary hemostasis and coagulation, as well as clinical projects (PedNet study group).

Publications

Schmidt DE, Michalopoulou A, Fischer K, Motwani J, Andersson NG, Pergantou H, et al. Long-term joint outcomes in adolescents with moderate or severe haemophilia A. *manuscript submitted*

Schmidt DE, Wendtland Edslev P, Heitink-Pollé KMJ, Kapur R, Porcelijn L, van der Schoot CE, et al. Age at Diagnosis Shapes the Prognosis of Childhood Immune Thrombocytopenia. medRxiv 2020. *manuscript submitted*

Wojcik IT*, **Schmidt DE***, de Neef LA, Rab M, Wuhrer M, van der Schoot CE, et al. A functional spleen contributes to afucosylated IgG in humans. Scientific Reports. 2021, *in print*. * *Authors contributed equally*

Schmidt DE, Heitink-Pollé KMJ, Mertens B, Porcelijn L, van der Schoot CE, Vidarsson G, et al. Biological stratification of clinical disease courses in childhood immune thrombocytopenia. Journal of Thrombosis and Hemostasis. 2021 Apr. DOI: 10.1111/jth.15232

Schmidt DE, Heitink-Pollé KMJ, Bruin MCA, de Haas M. Intravenous Immunoglobulins (IVIg) in Childhood Immune Thrombocytopenia: Towards Personalized Medicine - A Narrative Review. Annals of Blood. 2021 Mar 31. DOI: 10.21037/aob-20-59

Schmidt DE, Wendtland Edslev P, Heitink-Pollé KMJ, Mertens B, Bruin MCA, Kapur R, et al. A Novel Clinical Prediction Score for Transient Childhood Immune Thrombocytopenia. Journal of Thrombosis and Hemostasis. 2020 Oct 15. E-pub, DOI: 10.1111/jth.15125

Porcelijn L, **Schmidt DE**, Oldert G, Hofstede-van Egmond S, Kapur R, Zwaginga JJ, et al. Evolution and Utility of Antiplatelet Autoantibody Testing in Patients with Immune Thrombocytopenia. Transfusion Medicine Reviews. 2020 Sep 16. E-pub, DOI: 10.1016/j.tmrv.2020.09.003

Schmidt DE, Heitink-Pollé KMJ, Porcelijn L, van der Schoot CE, Vidarsson G, Bruin MCA, et al. Anti-Platelet Antibodies in Childhood Immune Thrombocytopenia: Prevalence and Prognostic Implications. Journal of Thrombosis and Hemostasis. 2020 Feb 13. E-pub, DOI: 10.1111/jth.14762

Schmidt DE, Lakerveld AJ, Heitink-Pollé KMJ, Bruin MCA, Vidarsson G, Porcelijn L, de Haas M. Platelet Autoantibody Immunoassays in Childhood Immune Thrombocytopenia: A Systematic Review. Vox Sanguinis. 2020 Feb 20. E-pub, DOI: 10.1111/vox.12894

Schmidt DE*, de Haan N*, Sonneveld ME, Porcelijn L, van der Schoot CE, de Haas M, et al. IgG-Fc glycosylation before and after rituximab treatment in immune thrombocytopenia. Sci Rep 10, 3051 (2020). DOI: 10.1038/s41598-020-59651-7 * *Authors contributed equally*

Strålfors A, Mikovic D, **Schmidt DE**, Onelöv L, Mahmoud Hourani Soutari N, Berndtson M, et al. Genetics and hemostatic potential in persons with mild to moderate hemophilia A with a discrepancy between one-stage and chromogenic FVIII assays. Thrombosis Haemostasis. 2020 Aug 13; E-pub. DOI: 10.1055/s-0040-1715443

Farm M, Antovic A, **Schmidt DE**, Bark N, Mahmoud Hourani Soutari N, Siddiqui AJ, et al. Diagnostic accuracy of thrombin generation and Overall Hemostatic Potential compared to D-dimer and Fibrin Monomers for acute venous thromboembolism. Thrombosis Haemostasis Open. 2020 Jul; 4(3): e178–e188. DOI 10.1055/s-0040-1714210

Schmidt DE, Heitink-Pollé KMJ, Laarhoven AG, Bruin MCA, Veldhuisen B, Nagelkerke SQ, et al. Transient and chronic childhood immune thrombocytopenia are distinctly affected by Fc-γ receptor polymorphisms. Blood Adv. 2019 Jul 9;3(13):2003–12.

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DOI: haematol.2019.228908. * *Authors contributed equally*

Rijkers M, **Schmidt D**, Lu N, Kramer CSM, Heidt S, Mulder A, et al. Anti-HLA antibodies with complementary and synergistic interaction geometries promote classical complement activation on platelets. Haematologica. 2019 Feb;104(2):403–16.

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