



Universiteit
Leiden
The Netherlands

Individualized prognosis in childhood immune thrombocytopenia

Schmidt, D.E.

Citation

Schmidt, D. E. (2022, April 7). *Individualized prognosis in childhood immune thrombocytopenia*. Retrieved from <https://hdl.handle.net/1887/3281832>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3281832>

Note: To cite this publication please use the final published version (if applicable).

DAVID SCHMIDT

INDIVIDUALIZED PROGNOSIS IN CHILDHOOD
IMMUNE THROMBOCYTOPENIA

INDIVIDUALIZED PROGNOSIS IN CHILDHOOD IMMUNE THROMBOCYTOPENIA

PROEFSCHRIFT

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 7 april 2022
klokke 13.45 uur
door

David Emanuel Schmidt
geboren te Bad-Nauheim in 1989.

PROMOTOR

Prof. dr. M de Haas

CO-PROMOTORES

Dr. MCA Bruin (UMC Utrecht - Prinses Maxima Centrum)

Dr. G Vidarsson (Amsterdam UMC - Sanquin)

PROMOTIECOMMISSIE

Prof. dr. JJ Zwaginga

Prof. dr. RHH Groenwold

Prof. dr. TWJ Huizinga

Dr. K Fischer (UMC Utrecht)

Prof. dr. TW Kuijpers (Amsterdam UMC)

Permission is granted to distribute copies of this document provided this notice remains intact. Financial support for printing: Sanquin Research, MRC Holland, ITP Patientenvereniging Nederland.

David Schmidt. *Individualized Prognosis in Childhood Immune Thrombocytopenia.*

© March 2022

Medicine is a science of uncertainty and an art of probability.
Sir William Osler (1849 - 1919)

Dedicated to my loving parents Trixi and Frieder,
and Rainer.

CONTENTS

I INTRODUCTION

1	Childhood Immune Thrombocytopenia	3
1.1	Morbidity and mortality	4
1.2	Disease mechanisms	4
1.3	Diagnosis	13
1.4	Prognosis	16
1.5	Clinical management	19
1.6	Treatment options	20
1.7	Modification of ITP disease courses	24
1.8	Towards individualized prognosis and treatment . . .	27
1.8.1	Proposed prediction markers of ITP disease courses	27
1.9	Statistical learning	33
1.10	Research questions and scope of the thesis	37

II GENETIC AND IMMUNE PARAMETERS FOR PROGNOSIS

2	Age at diagnosis shapes the prognosis of childhood ITP.	41
3	Transient and chronic childhood immune thrombocytopenia are distinctly affected by Fc- γ receptor polymorphisms.	65
4	Platelet autoantibody immunoassays in childhood ITP: a systematic review.	85

5	Antigen-specific autoantibodies indicate prognosis and IVIg treatment response in childhood immune thrombocytopenia.	113
6	ITGB1-expressing CD4 ⁺ T effector cell response associates with chronic childhood immune thrombocytopenia.	127
III PATHOPHYSIOLOGY AND MECHANISMS OF ITP		
7	IgG-Fc glycosylation before and after rituximab treatment in immune thrombocytopenia.	163
8	Anti-glycoprotein Ib α autoantibodies do not impair circulating thrombopoietin levels in immune thrombocytopenia patients.	173
IV MODELS FOR PROGNOSTICATION		
9	A clinical prediction score for transient versus persistent childhood immune thrombocytopenia.	179
10	Biological stratification of clinical disease courses in childhood immune thrombocytopenia.	195
11	Intravenous Immunoglobulins (IVIg) in childhood immune thrombocytopenia: towards personalized medicine.	229
V DISCUSSION		
12	General discussion	243
12.1	Prediction models for ITP prognosis	244
12.1.1	Individualized prediction of ITP spontaneous recovery and IVIg treatment responses	247
12.2	Insights into ITP pathophysiology	252
12.2.1	Genetic heterogeneity	252

12.2.2	Platelet autoantibodies	253
12.2.3	Cellular immune response	254
12.2.4	Age heterogeneity	256
12.2.5	Further thoughts on mechanisms	257
12.3	Clinical implications	259
12.3.1	Diagnosis of ITP	259
12.3.2	Prognosis versus diagnosis	260
12.3.3	Additional diagnostic tests	261
12.3.4	Treatment	263
12.3.5	Questions of generalizability	264
12.3.6	Follow-up studies	264
12.4	A roadmap to advance ITP research & care	266
12.4.1	Dogmalysis	266
12.4.2	Better clinical study design	268
12.4.3	Focus on patient-centered outcomes	270
12.4.4	Towards a reporting standard	270
13	Conclusions	273
VI APPENDIX		
a	Definitions	277
b	Bibliography	281
c	PhD Portfolio	299
d	Curriculum vitae	301
e	Dutch Summary	307
	Acknowledgments	311

