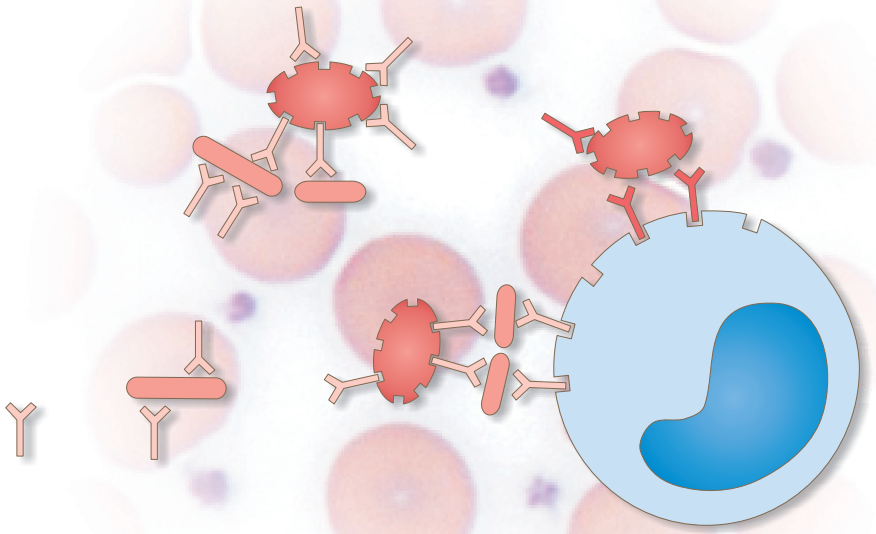
Immune Thrombocytopenia (ITP)

3rd edition

Thomas Kühne

in collaboration with
Carlo L. Balduini, Carolyn E Beck,
George R. Buchanan, James B. Bussel,
Andrew R. Crow, Yoelys Cruz-Leal,
Samuel Deshayes, Terry B. Gernsheimer,
Waleed Ghanima, Lazaro Gil,
Bertrand Godeau, Paul Imbach,
Robert Klaassen, Michele P. Lambert,
Alan H. Lazarus, Joel Livingston,
Axel C. Matzdorff, Adrian Newland,
Peter A.A. Norris, Alessandro Pecci,
Francesco Rodeghiero, Alexandra Schifferli,
John W. Semple, Zoya Tawhidi,
Kevin D. Won, James L. Zehnder



UNI-MED

SCIENCE

Immune Thrombo-cytopenia (ITP)

UNI-MED

UNI-MED Verlag AG
Bremen - London - Boston

Kühne, Thomas:
Immune Thrombocytopenia (ITP)/Thomas Kühne.-
3rd edition - Bremen: UNI-MED, 2022
(UNI-MED SCIENCE)
ISBN 978-3-8374-5624-0

MEDICINE - STATE OF THE ART

UNI-MED Verlag AG, one of the leading medical publishing companies in Germany, presents its highly successful series of scientific textbooks, covering all medical subjects. The authors are specialists in their fields and present the topics precisely, comprehensively, and with the facility of quick reference in mind. The books will be most useful for all doctors who wish to keep up to date with the latest developments in medicine.

The publisher would like to thank the company Swedish Orphan Biovitrum for supporting the production of this edition. The publisher assures that the industry partner could not influence the content of the book in any way, especially not therapy recommendations.

Preface to the 3rd edition

In recent years there was much movement in the area of immune thrombocytopenia (ITP). There is increasing knowledge in the understanding how platelets function and what is wrong with them under pathological conditions. It has been realized that platelets are not only cells involved in hemostatic processes, but also act in innate and adaptive immune responses and exert inflammatory functions. ITP occurs as a result of dysregulated immune responses based on probably many different mechanisms, which may cause thrombocytopenia as a result of an increased and premature destructive process of platelets and a disturbed mega- and thrombopoiesis. This destructive process may evolve into therapy-refractoriness ("autoimmune expansion") in certain patients that is not predictable. Our clinical observations and assessments of platelet counts however do not tell us clearly neither the bleeding risk of a given patient, nor his or her disease course. This may be due to the fact that there is usually absence of individual information of ITP pathomechanisms and that bleeding is a complex process influenced by intrinsic and extrinsic factors affecting platelet production and function. This complexity is the reason why ITP exhibits a strong clinical inter- and intra-patient variability with unpredictable response to therapies and thus demands for individual solutions. Moreover, there is increasing knowledge of symptoms other than bleeding, such as fatigue and reduced health-related quality of life, which may represent treatment endpoints and reflect patients' needs. Based on this knowledge new diagnostic and therapeutic strategies will be developed from which patients hopefully will benefit.

Elucidation of molecular pathways and targets and their disturbances are the basis for the development of new therapies, similarly to other areas in medicine. This process will probably continue with the aim for treating so-called targets reflecting the desire for tolerable, efficient and curative treatments for all patients without side effects and complications and development of strict patient selection criteria. We are far away from this ideal concept, but we may increasingly be aware of the way how to approach this ideal.

The third edition of this book attempts to reflect this departure into future time without omitting current scientific knowledge and clinical practice of children and adults with ITP. The material of ITP became so complex and substantial in recent years, that a comprehensive book would need much more time and volume. The current edition was written in a difficult time reflected by the COVID-19 pandemic with many obstacles and adversities. I would like to express my deep gratitude to all co-authors who worked hard on this edition and who contributed to the successful completion of this book. It was a real and great pleasure to collaborate with them and to see the book growing. I would like to thank the publisher UNI-MED Verlag Bremen, who always supported me, never lost patience and always demonstrated interest in this book project. I hope that this new edition contributes to optimal patient care and management.

Basel, January 2022 *Thomas Kühne*

Authors

Carlo L. Balduini
Ferrata-Storti Foundation
Pavia
Italy

Chapter 6.

Carolyn E Beck, MD, MSc, FRCPC
Associate Professor
Faculty of Medicine
University of Toronto
Division of Paediatric Medicine, Department of Paediatrics
The Hospital for Sick Children
Toronto
Ontario, Canada

Chapter 9.

George R. Buchanan, MD
Division of Hematology-Oncology
Center for Cancer and Blood Disorders
Children's Medical Center and
University of Texas Southwestern Medical Center
Dallas, Texas
USA

Chapter 20.

James B. Bussel, MD
Department of Pediatrics
Weill Medical College
525 East 68th Street P-695
New York NY 10021
USA

Chapter 13.

Andrew R. Crow, BRT
Transfusion Medicine Research
St. Michael's Hospital
30 Bond Street
Toronto, Ontario
Canada, M5B 1W8

Chapter 15.

Yoelys Cruz-Leal
Centre for Innovation
Canadian Blood Services
Ottawa, ON
Canada

Keenan Research Centre for Biomedical Science
St. Michael's Hospital
Unity Health Toronto
Toronto ON
Canada

Toronto Platelet Immunobiology Group
Toronto, ON
Canada

Chapter 16.

Samuel Deshayes
Service de médecine interne
CHU de Caen Normandie
Avenue de la Côte de Nacre
14033 Caen Cedex
France

Chapter 11.

Terry B. Gernsheimer, MD
Professor of Medicine and Hematology
University of Washington
Puget Sound Blood Center
Seattle
USA

Chapter 14.

Waleed Ghanima
Consultant Hematologist
Professor, Institute of Clinical Medicine
Østfold Hospital
University of Oslo, Norway

Chapter 12.

Lazaro Gil
Keenan Research Centre for Biomedical Science
St. Michael's Hospital
Unity Health Toronto
Toronto ON
Canada

Toronto Platelet Immunobiology Group
Toronto, ON
Canada

Chapter 16.

Bertrand Godeau, MD
Service de médecine interne
Centre labellisé de référence pour la prise en charge et la recherche
sur les cytopénies auto-immunes de l'adulte
Centre Hospitalier Universitaire Henri-Mondor
Assistance Publique-Hôpitaux de Paris
Université Paris Est Créteil
51, avenue du Maréchal-de-Lattre-de-Tassigny
94010 Créteil cedex
France

Chapter 11.

Paul Imbach, MD
Division of Oncology/Haematology
University Children's Hospital
Postfach
Römergasse 8
CH-4005 Basel
Switzerland

Chapter 2., 21.

Robert Klaassen, MD, FRCP(C)
Professor, Department of Pediatrics
Division of Hematology/Oncology
Department of Pediatrics
University of Ottawa
Children's Hospital of Eastern Ontario
Ottawa
Ontario, Canada

Chapter 9., 18.

Thomas Kühne, MD
Division of Oncology/Haematology
University Children's Hospital
Postfach
Römergasse 8
CH-4005 Basel
Switzerland

Chapter 1., 10.

Michele P. Lambert, MD, MSTR
The Children's Hospital of Philadelphia
Division of Hematology, Philadelphia, PA
Perelman School of Medicine
University of Pennsylvania
Department of Pediatrics
Philadelphia, PA

Chapter 4.

Alan H. Lazarus
Centre for Innovation
Canadian Blood Services
Ottawa, ON
Canada

Department of Laboratory Medicine and Pathobiology
University of Toronto
Toronto, ON
Canada

Keenan Research Centre for Biomedical Science
St. Michael's Hospital
Unity Health Toronto
Toronto ON
Canada

Toronto Platelet Immunobiology Group
Toronto, ON
Canada

Department of Medicine
University of Toronto
Toronto, ON
Canada

Chapter 15., 16.

Joel Livingston MSc, MD, FRCPC
Clinical Fellow
Division of Haematology/Oncology
Department of Paediatrics
University of Toronto
The Hospital for Sick Children, Toronto
Ontario
Canada

Chapter 18.

Axel C. Matzdorff, MD, PhD
Director Dpt. of Hematology, Oncology, Hemostasis
Caritasklinikum Saarbruecken St. Theresia
Rheinstrasse 2
66113 Saarbrücken
Germany

Chapter 17.

Adrian Newland, CBE
Professor of Haematology
Barts and The London School of Medicine and Dentistry
Queen Mary University of London
London, UK
Email: a.c.newland@qmul.ac.uk

Chapter 19.

Peter A.A. Norris
Centre for Innovation
Canadian Blood Services
Ottawa, ON
Canada

Department of Laboratory Medicine and Pathobiology
University of Toronto
Toronto, ON
Canada

Keenan Research Centre for Biomedical Science
St. Michael's Hospital
Unity Health Toronto
Toronto ON
Canada

Toronto Platelet Immunobiology Group
Toronto, ON
Canada

Chapter 16.

Alessandro Pecci
University of Pavia
IRCCS Policlinico San Matteo Foundation
Pavia
Italy

Chapter 6.

Francesco Rodeghiero, MD
Department of Cell Therapy and Haematology
San Bortolo Hospital
Vicenza
Italy

Chapter 8.

Alexandra Schifferli
Department of Oncology/Hematology
University Children's Hospital Basel
Spitalstrasse 33
CH-4031 Basel, Switzerland

Chapter 7.

John W. Semple, PhD
Professor of Transfusion Medicine
Division of Hematology and Transfusion Medicine
Lund University
Clinical Immunology and Transfusion Medicine
Office of Medical Services
Region Skåne
Lund
Sweden

Chapter 3.

Zoya Tawhidi
Department of Laboratory Medicine and Pathobiology
University of Toronto
Toronto, ON
Canada

Keenan Research Centre for Biomedical Science
St. Michael's Hospital
Unity Health Toronto
Toronto ON
Canada

Toronto Platelet Immunobiology Group
Toronto, ON
Canada

Chapter 16.

Kevin D. Won
Department of Laboratory Medicine and Pathobiology
University of Toronto
Toronto, ON
Canada

Keenan Research Centre for Biomedical Science
St. Michael's Hospital
Unity Health Toronto
Toronto ON
Canada

Toronto Platelet Immunobiology Group
Toronto, ON
Canada

Chapter 16.

James L. Zehnder, MD
Professor of Pathology and Medicine (Hematology)
Director of Clinical Pathology, Department of Pathology
Stanford University School of Medicine
Director, Coagulation and Molecular Genetic Pathology Laboratories
Stanford Health Care
USA

Chapter 5.

Contents

1. Introduction

"Immune thrombocytopenia" (ITP) was proposed by an international working group at the Vicenza Consensus Conference to be more appropriate than "idiopathic thrombocytopenic purpura" or "immune thrombocytopenic purpura", because of the immune-mediated mechanisms and because not all patients with ITP present with a purpura [1]. Furthermore, ITP was proposed by the same group to be classified as primary and secondary ITP. Primary ITP, formerly called idiopathic thrombocytopenic purpura, indicates absence of the knowledge of any initiating or underlying causes for thrombocytopenia and is the main topic of this book. Secondary ITP reflects immune mediated thrombocytopenia with a known cause, such as an infectious disease, lymphoproliferation, systemic lupus erythematosus, immune deficiency and other disorders, and is described elsewhere [2-5]. There is growing knowledge of secondary ITP both in children and adults [6, 7], particularly demonstrated by the SARS-CoV-2 pandemic.

Thrombocytopenia (platelet count $<100 \times 10^9$/L) is caused by premature platelet and megakaryocyte destruction by the monocytic-phagocytic system, which results in reduced survival of platelets, structural changes of platelets and their function, and in potential bleeding with a wide range of unpredictable clinical variability, from no or oligosymptomatic patients to severe fatal bleeding.

Mild and moderate bleeding, defined differently in the literature, is frequent, whereas severe fatal bleeding, such as intracranial haemorrhage, is rare in childhood and increases with age. Several reasons may be responsible for the variability and severity of bleeding, such as age of the patient, acquired and congenital co-morbidities, i.e. environmental and predisposing genetic factors, and drugs. Thrombocytopenia reflecting the key feature of ITP is the result of complex and not well-characterized various mechanisms involving the innate and adaptive immune system, the hematopoiesis, inflammatory system, and various regulatory systems. The classical pathophysiology with autoantibodies opsonizing platelets with their subsequent Fc-mediated phagocytosis is not always present. It is estimated that approximately one third of adult patients with ITP lack autoantibodies. Furthermore, autoimmunity represents a dynamic process with the potential of autoimmune expansion and epitope spreading, which may explain at least in part that chronic ITP may become therapy-refractory. Thus, an etiological background remains often unknown, which defines primary ITP. This unknown background of primary ITP must be taken into consideration when evaluating results of clinical trials. Despite rigorous inclusion and exclusion criteria, trial populations consist of individuals with a potentially highly heterogeneous pathophysiological background. This can be demonstrated when evaluating early cohort studies, which included patients with malignancies or patients treated with acetylsalicylic acid. Since the description of a patient with suspected "ITP" by Paul Gottlieb Werlhof in 1735 [8], basic science and clinical research have revealed many different acquired and inherited causes for thrombocytopenia, which cannot be classified as ITP based on modern definitions. Thus, the group of patients with primary ITP becomes steadily smaller during time. Primary ITP remains still a mystery and clinicians and researchers should be encouraged to critically use the diagnosis "primary ITP" and to continuously consider the large list of differential diagnoses. ITP may be simply considered as a symptom, rather than a "disease" ("Werlhof's disease"). The heterogeneity of ITP is a basis for controversies regarding pathophysiology and management of patients with ITP, and this unclear background is further fuelled by a substantial lack of knowledge of basic science and clinical research.

Lack of evidence and controversial management resulted in the establishment of various groups who developed national and international practice guidelines, which initially were based mainly on expert opinion and consensus conferences, rather than on evidence [9-13]. Although guidelines are appropriate and important tools to manage patients with ITP, there are also limitations, as critical questions have been asked, and as it has been shown that guidelines are not consistently followed [14-17]. Why is that? First of all, as it has

been mentioned above, primary ITP is still a diagnosis of exclusion with the consequence, that the population of patients diagnosed with primary ITP represents a heterogeneous group causing difficulties in analyzing study results and drawing conclusions. Guidelines are not based solely on clinical evidence, demonstrated by George et al. [10], rather they reflect expert and consensus opinions based on relatively few clinical randomized trials, which are furthermore characterized by short follow-up time and frequently designed for objectives, which differ from objectives and their interpretations made in guidelines. These are reasons why there are various guidelines and why they are not consistent and even contradict each other in certain statements. Furthermore, they may not reflect the opinion of doctors working at "the front", because of different local circumstances, differences in availability of drugs and last but not least the complexity of such guidelines [11]. However, the development of guidelines stimulated a systematic and coordinated approach to the problems associated with ITP. With the development of thrombopoietin-receptor agonists, evidence-based medicine with strict criteria was introduced. Comprehensive and critical appraisal of the literature became the basis for an appropriate approach to and management of the patient with ITP, and optimization of research coordination including economical use of resources became goals of international activities.

Despite the difficulties associated with primary ITP many achievements have been made in recent years and will be discussed in this book, including growing knowledge in immunology, hemato- and megakaryopoiesis, platelet physiology, genetic aspects of autoimmune diseases, and pharmacology. Clinical achievements include a harmonization of terminology, definitions and outcome criteria [1], international activity in developing guidelines [11] and in coordinating research and communication, such as the Pediatric and Adult Registry on Chronic ITP (PARC-ITP) of the Intercontinental Cooperative ITP Study Group (ICIS, www.itpbasel.ch) and many other groups, and clearly the development of new drugs in recent years, such as monoclonal anti-CD20 antibodies, e.g., rituximab, and thrombopoietin receptor agonists, e.g., romiplostim, eltrombopag, avatrombopag, as well as fostamatinib, and drugs under development, such as FcRn-antagonists, BTK inhibitors, complement inhibitors and others. These new drugs created a new and fresh wind, which blows into algorithms and guidelines, resulting in new strategies of the management of patients with ITP. However, although the armamentarium of therapeutic interventions for such patients has been enriched with powerful new drugs, many scientific questions need to be answered and the exact clinical

Problems in ITP
• Unknown etiology of primary ITP
• Primary ITP as a diagnosis of exclusion
• Difficulties in combining basic science and clinical research
• Predictability of chronic symptomatic ITP and of therapy refractory ITP
• Difficulty in estimation of individual bleeding risk
• Poorly defined endpoints and the use of the platelet count as treatment endpoint in the management of patients with ITP and in clinical trials
• Lack of validation of alternative treatment endpoints, such as bleeding, fatigue, health-related quality of life, adverse effects of platelet-enhancing drugs, and economical aspects
• Poorly defined prevention and treatment interventions of bleeding resulting in confusing assessments of their clinical benefit
• Substantial lack of investigator-driven clinical randomized trials and of real world data
• Substantial lack of knowledge of long-term natural history of ITP and long-term aspects after medical intervention, such as drugs and splenectomy
• Strategy of the management with novel drugs
• Integration of patients' needs and requirements and their voice in developing management strategies

Table 1.1: Problems in ITP (incomplete list).

strategical position of these drugs continues to await clarification. Furthermore, in developing new therapies and new management tools including practice guidelines it is important to integrate the patients' voice, in order to balance medical desires and treatment endpoints, as well as the patient's perspective and their needs [18].

As the world is becoming smaller and obstacles to collaborate are encountered less frequently, international activities become more feasible with the potential to overcome problems associated with rare diseases. Large numbers of patients can be approached better and faster, coordination of research may include many countries, and national borders may become conquerable with powerful communication tools to exchange study results within adequate time. There is, however, still a long list of substantial problems associated with ITP (☞ Table 1.1), which needs energy, courage, and investment for the realization of basic science and clinical research projects, but also for further improvement of international communication and coordination of resources and activities. Immune thrombocytopenia remains an attractive model disorder for autoimmunity and its treatment, in order to restore tolerance.

References

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura (ITP) of adults and children. Report from an international working group. Blood 2009;113:2386-2393.

2. Liebman HA, Stasi R. Secondary immune thrombocytopenic purpura. Curr Opin Hematol. 2007;14:557-573.

3. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood. 2009;113:6511-6521.

4. Bussel JB. Therapeutic approaches to secondary immune thrombocytopenic purpura. Semin Hematol. 2009;46(Suppl 2):S44-58.

5. Kim TO, Despotovic JM. Primary and Secondary Immune Cytopenias Evaluation and Treatment Approach in Children. Hematol Oncol Clin N Am. 2019;33:489-506.

6. Schifferli A, Heiri A, Imbach P, et al. Misdiagnosed thrombocytopenia in children and adolescents: analysis of the Pediatric and Adult Registry on Chronic ITP. Blood Adv. 2021;5(6):1617-1626.

7. Michel M, Lega J-C, Terriou L. [Secondary ITP in adults] [Article in French]. Rev Med Interne. 2021;42(1):50-57

8. Werlhof PG. De Variolis et Anthracibus. Hannover, 1735

9. Eden OB, Lilleyman JS Guidelines for management of idiopathic thrombocytopenic purpura. The British Paediatric Haematology Group. Arch Dis Child. 1992;67:1056-1058.

10. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for The American Society of Hematology. Blood. 1996;88:3-40.

11. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3(22):3780-3817.

12. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia [published correction appears in Blood Adv. 2020;4(2):252]. Blood Adv. 2019;3(23):3829-3866.

13. Matzdorff A, Meyer O, Ostermann H, et al. Immune Thrombocytopenia – Current Diagnostics and Therapy: Recommendations of a Joint Working Group of DGHO, ÖGHO, SGH, GPOH, and DGTI. Oncol Res Treat 2018;(41 Suppl 5):1-30

14. Buchanan GR, de Alarcon PA, Feig SA, et al. Acute idiopathic thrombocytopenic purpura – management in childhood. Blood. 1997;89:1464-1465

15. Bolton-Maggs PHB, Moon I. Assessment of UK practice for management of acute childhood idiopathic thrombocytopenic purpura against published guidelines. Lancet 1997;350:620-623

16. Vesely S, Buchanan GR, Cohen A, et al. Self-reported diagnostic and management strategies in childhood idiopathic thrombocytopenic purpura: results of a survey of practicing pediatric hematology/oncology specialists.J Pediatr Hematol Oncol 2000;22:55-61

17. Matzdorff A, Arnold G. Treatment of chronic immune thrombocytopenic purpura: the patients' perspective. Eur J Haematol 2007;78:381-388

18. Terrell DR, Neunert CE, Cooper N, et al. Immune Thrombocytopenia (ITP): Current Limitations in Patient Management. Medicina 2020;56(12), 667

2. History of ITP

2.1. Introduction: What is thrombocytopenic bleeding?

Immune thrombocytopenia (ITP) is characterized by isolated destruction of platelets. Susceptible individuals are recognized with a low platelet count. Some of them demonstrate easy bruising, petechiae, suffusions, nose bleedings and rarely severe bleeding including hematuria, gastrointestinal bleeding, prolonged menstruation, and central nervous bleeding [1, 2] (☞ Table 2.1).

Bleeding Grade Classification [20]	Bolton-Maggs & Moon % (n=427)	ICIS Registry II % (n=863)
None/mild	76% (324)	77% (665)
Moderate	21% (90)	20% (173)
Severe	3% (13)	3% (25)*

Table 2.1: Comparison of bleeding severity based on strict definitions of bleeding and bleeding scores by different authors. *Sites of bleeding (some with more than one site): epistaxis (15 cases), mouth (8 cases), gastrointestinal tract (8 cases), urinary tract (2 cases), multiple sites (12 cases), other (1 case), and menorrhagia and nervous system (1 case each).

For example, in the Intercontinental Cooperative ITP Study Group (ICIS) Registry II, 665 of 883 (70%) children with newly diagnosed ITP and a platelet count below 20 x 10^9/L had no or mild bleeding at presentation, 173 (20%) had moderate bleeding, and 25 (3%) had severe bleeding. Bleeding was categorized as

(1) *none or mild*: no bleeding at all or bruising, petechiae, occasional mild epistaxis causing very little or no interference with daily living;

(2) *moderate*: more severe skin manifestations with some mucosal lesions and more troublesome epistaxis or menorrhagia; or

3) *severe*: bleeding episodes (epistaxis, melena, menorrhagia, and/or intracranial hemorrhage) requiring hospital admission and/or blood transfusions, i.e., symptoms interfering seriously with quality of life [3, 4].

The susceptibility of ITP is unknown. ITP often occurs as a para- or postinfectious event, which may indicate disturbed recovery of the subject's immune system. Most of these patients have a transient form of ITP. In other patients ITP is ongoing for 3 to 12 months (persistent ITP) or more than 12 months (chronic ITP). In persistent or chronic, secondary ITP may be present and a differential diagnosis must be performed (☞ Table 2.2).

Primary ITP	80 %
Para-/postinfectous (children)	(70 %)
Postvaccinal (children)	(1.2%)
Secondary ITP	20 %
Systemic Lupus Erythematosus (SLE)	5 %
Hepatitis C	3 %
Helicobacter pylori	2 %
Systemic infections	2 %
Antiphospholipid Syndrome (APS)	2 %
Evans Syndrome	2 %
Chronic Lymphocytic Leukemia (CLL)	2 %
Common Variable Immune Deficiency (CVID)	1 %
Human Immunodeficiency Virus Infection	1 %

Table 2.2: Short list of the differential diagnosis of primary and secondary ITP.

Pathophysiologically the severity of bleeding in patients with ITP reflects the balance between platelet production by megakaryocytes and the accelerated clearance of antibody-sensitized platelets. The antibodies are directed against specific epitopes on platelet glycoproteins (specific autoantibodies) or may be crossreactive, unspecific antibodies or immune complexes. The latter are mainly discussed in transient, postinfectious ITP.

The largest group of patients with thrombocytopenia are patients with cancer or autoimmune disorders under immunosuppressive treatment (chemotherapy, radiotherapy) leading to transient megakaryocyte suppression resulting in low platelet production as adverse effect. The group of patients is not included in this chapter.

2.2. History of bleeding

Bleeding signs are fearful for the patient and may disturb the quality of life of an individual. Since more than 2500 years bleeding was described and attempts made for resolvement.

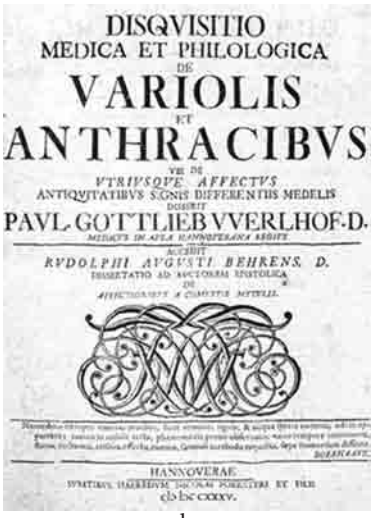
During the Greek and Roman period beginning 700 years BCE spontaneous cutaneous bleeding has been named purpura, deduced from the greek porphyra which signifies the purple dye, secreted by the purple snail, used as status symbol during antiquity and the Middle Age. There was no knowledge of the different blood components and functions at that time.

In 1557 the Portuguese Amatus Lusitanus mentioned a condition *Morbus pulicaris absque fibre* (without fever). In his work *Curationum medicinalum* he describes "… a boy with dark macules, resembling flea bites, had no fever and for several days had bloody discharges, eventually recovering". His description could have been thrombocytopenic bleeding.

In the early seventeenth century, Riverius (Lazarus de la Rivière) in his *Praxis medica* mentioned "the spots arisen from the over thinness of the blood … does sprout forth of the capillary veins into the skin … where being retained, it looseth its own colour, and becomes either blewish or black, or light red, and causes great variety of spots…" [5].

In 1775 Paul Werlhof [6] (☞ Figure 2.1a) a poet, composer, linguist and physician described the disorder under the name of *Morbus Maculosus Haemorhhagicus*. He became physician to King George II of England, at the same time elector of Hannover. In his book *De Variolis et Anthracibus* (☞ Figure 2.1b) [7] he mentioned in a footnote a 16-year-old girl with cutaneous and mucosal bleeding which occurred after an infectious disease and recovered after Elixirium acidum Halleri (citric acid). The name of the elixir refers to Albrecht von Haller, famous Swiss physician, botanist and poet, who was professor at the University of Göttingen, where he contacted Werlhof.

a



b

Figure 2.1a+b: **a**: Paul Gottlieb Werlhof. **b**: First page of his book *De Variolis et Anthracibus* (1735; with acknowledgement to Professor G. Gaedicke, Berlin, 1990).

The next milestone was the observation of a similar disorder by Dohrn in 1873 in a neonate and his mother. The term "platelets" was first used by Kraus 1883 [8] and Deny 1897 [9], who observed that platelets were diminished during the height of the purpura and increased when hemorrhage ceased. These findings were confirmed by Hayem [10] in 1895 who performed more accurate platelet counts.