

# Contents

|                                                                                    |                                                                                                                |           |
|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------|
|    | <b>Introduction</b>                                                                                            | <b>18</b> |
|    | <b>History of ITP</b>                                                                                          | <b>21</b> |
| 2.1.                                                                               | Introduction: What is thrombocytopenic bleeding? .....                                                         | 21        |
| 2.2.                                                                               | History of bleeding .....                                                                                      | 22        |
| 2.3.                                                                               | History of the pathogenesis of ITP .....                                                                       | 23        |
| 2.4.                                                                               | History of management of patients with ITP .....                                                               | 23        |
| 2.5.                                                                               | The therapeutic translation of IVIg to other autoimmune disorders with similar pathophysiology as in ITP ..... | 25        |
| 2.6.                                                                               | Stimulation of platelet production by megakaryocytes .....                                                     | 26        |
| 2.7.                                                                               | Recent development of clinical research of ITP and new aspects of platelets themselves ...                     | 27        |
|    | <b>Basic immunology of ITP</b>                                                                                 | <b>30</b> |
| 3.1.                                                                               | T cell and cytokine abnormalities in ITP .....                                                                 | 30        |
| 3.2.                                                                               | B cell abnormalities .....                                                                                     | 31        |
| 3.3.                                                                               | Dendritic Cells (DC) in ITP .....                                                                              | 31        |
| 3.4.                                                                               | Environmental factors in ITP .....                                                                             | 32        |
| 3.5.                                                                               | Alternative modes of thrombocytopenia in ITP .....                                                             | 33        |
| 3.6.                                                                               | Conclusions .....                                                                                              | 33        |
|    | <b>Megakaryopoiesis in ITP</b>                                                                                 | <b>36</b> |
| 4.1.                                                                               | Overview of normal thrombopoiesis .....                                                                        | 36        |
| 4.2.                                                                               | Thrombopoiesis in ITP: evidence for accelerated platelet destruction .....                                     | 38        |
| 4.3.                                                                               | Thrombopoiesis in ITP: evidence for impaired platelet production .....                                         | 39        |
| 4.4.                                                                               | Megakaryopoiesis in ITP: evidence for direct roles of megakaryocytes .....                                     | 40        |
|  | <b>Genetics of ITP</b>                                                                                         | <b>45</b> |
| 5.1.                                                                               | Challenges in defining a genetic etiology of ITP .....                                                         | 45        |
| 5.2.                                                                               | Germline single-nucleotide variant (SNV) candidate gene approach .....                                         | 45        |
| 5.3.                                                                               | Familial ITP .....                                                                                             | 45        |
| 5.4.                                                                               | Genome-wide association studies (GWAS) .....                                                                   | 46        |
| 5.5.                                                                               | Future Directions .....                                                                                        | 47        |
|  | <b>Differential diagnosis of ITP: Inherited Thrombocytopenias</b>                                              | <b>48</b> |
| 6.1.                                                                               | Inherited Thrombocytopenias .....                                                                              | 48        |
| 6.1.1.                                                                             | Clinical and laboratory peculiarities of inherited thrombocytopenias .....                                     | 48        |
| 6.1.2.                                                                             | When to suspect inherited thrombocytopenias .....                                                              | 54        |
| 6.2.                                                                               | Differential diagnosis between ITP and inherited thrombocytopenias .....                                       | 55        |
| 6.3.                                                                               | How to confirm the suspicion of inherited thrombocytopenia .....                                               | 57        |
|  | <b>Secondary ITP</b>                                                                                           | <b>59</b> |
| 7.1.                                                                               | Definition and limitation .....                                                                                | 59        |
| 7.2.                                                                               | Etiology .....                                                                                                 | 59        |
| 7.3.                                                                               | Diagnostic workflow .....                                                                                      | 60        |

|            |                                                                                                       |            |
|------------|-------------------------------------------------------------------------------------------------------|------------|
| 7.4.       | Genetic panel.....                                                                                    | 62         |
| 7.5.       | Adult versus children .....                                                                           | 62         |
| 7.6.       | Conclusions .....                                                                                     | 64         |
| <b>7.</b>  | <b>Standardization of definitions, terminology and outcome criteria:<br/>a common language in ITP</b> | <b>67</b>  |
| 8.1.       | Criteria adopted by the IWG to harmonize terminology and definitions in ITP.....                      | 68         |
| 8.2.       | Primary and secondary ITP and diagnostic platelet count threshold .....                               | 68         |
| 8.3.       | Definition of the different phases and severity of the disease .....                                  | 69         |
| 8.4.       | Therapeutic goals.....                                                                                | 70         |
| 8.5.       | Definition of response .....                                                                          | 71         |
| 8.6.       | Refractory ITP: definition, therapeutic goals and response assessment .....                           | 73         |
| 8.7.       | Clinical trial-adapted criteria for eligibility and outcome assessment.....                           | 75         |
| 8.8.       | Application of 2009 IWG proposals in real-word and need for revision .....                            | 75         |
| 8.9.       | Conclusions .....                                                                                     | 75         |
| <b>8.</b>  | <b>Decision making in the management of children with ITP</b>                                         | <b>80</b>  |
| 9.1.       | A preference-sensitive decision .....                                                                 | 80         |
| 9.2.       | Shared decision making.....                                                                           | 81         |
| 9.3.       | Conclusion .....                                                                                      | 81         |
| <b>9.</b>  | <b>ITP in childhood: a problem-oriented review of the management</b>                                  | <b>84</b>  |
| 10.1.      | Clinical presentation and diagnosis.....                                                              | 85         |
| 10.2.      | Prevention from and therapy of bleeding.....                                                          | 87         |
| 10.3.      | Non-intervention .....                                                                                | 88         |
| 10.4.      | Intervention .....                                                                                    | 88         |
| 10.5.      | Splenectomy .....                                                                                     | 90         |
| 10.6.      | Conclusions .....                                                                                     | 90         |
| <b>10.</b> | <b>ITP in adulthood</b>                                                                               | <b>93</b>  |
| 11.1.      | Treatment of adult ITP .....                                                                          | 94         |
| 11.1.1.    | General rules.....                                                                                    | 94         |
| 11.1.2.    | First-line therapy (initial treatment for newly diagnosed patients).....                              | 94         |
| 11.1.3.    | Second-line therapy.....                                                                              | 95         |
| 11.1.4.    | Other second-line therapies .....                                                                     | 97         |
| 11.1.5.    | Patients failing multiple therapies.....                                                              | 99         |
| 11.1.6.    | New second- or third- or later-line therapies in the management of adults with ITP.....               | 100        |
| 11.2.      | Conclusion .....                                                                                      | 101        |
| <b>11.</b> | <b>Management of ITP in the elderly</b>                                                               | <b>105</b> |
| 12.1.      | Diagnosis of ITP in the elderly .....                                                                 | 105        |
| 12.2.      | Treating ITP in the elderly .....                                                                     | 105        |
| 12.2.1.    | Intravenous immunoglobulins (IVIg).....                                                               | 106        |
| 12.2.2.    | Corticosteroids.....                                                                                  | 106        |
| 12.2.3.    | Managing treatment failure and corticosteroid dependency.....                                         | 106        |
| 12.2.4.    | Thrombopoietin receptor agonists .....                                                                | 106        |
| 12.2.5.    | Rituximab.....                                                                                        | 107        |

|            |                                                                                 |            |
|------------|---------------------------------------------------------------------------------|------------|
| 12.2.6.    | Fostamatinib .....                                                              | 108        |
| 12.2.7.    | Splenectomy .....                                                               | 108        |
| 12.2.8.    | Other medications .....                                                         | 108        |
| 12.2.9.    | Investigational therapies .....                                                 | 108        |
| <b>13.</b> | <b>Chronic refractory ITP</b> .....                                             | <b>110</b> |
| 13.1.      | Practical Considerations of Refractory ITP .....                                | 110        |
| 13.2.      | Infection-related thrombocytopenia .....                                        | 113        |
| 13.3.      | Drug-induced thrombocytopenia .....                                             | 115        |
| 13.4.      | Secondary ITP .....                                                             | 115        |
| 13.5.      | Therapeutic approach .....                                                      | 116        |
| 13.5.1.    | General approach to refractory ITP .....                                        | 117        |
| 13.5.1.1.  | Observation .....                                                               | 117        |
| 13.5.1.2.  | Standard therapy .....                                                          | 117        |
| 13.5.1.3.  | Therapy for refractory disease .....                                            | 117        |
| 13.6.      | Outcomes and sequelae .....                                                     | 121        |
| 13.7.      | Summary .....                                                                   | 122        |
| <b>14.</b> | <b>Immune thrombocytopenia in pregnancy</b> .....                               | <b>127</b> |
| 14.1.      | The differential diagnosis of thrombocytopenia during pregnancy .....           | 127        |
| 14.2.      | ITP in pregnancy .....                                                          | 128        |
| 14.3.      | Conclusion .....                                                                | 130        |
| <b>15.</b> | <b>Drugs in ITP: mechanisms of action</b> .....                                 | <b>133</b> |
| 15.1.      | Steroids .....                                                                  | 133        |
| 15.2.      | Intravenous immunoglobulin (IVIg) .....                                         | 134        |
| 15.3.      | Anti-D .....                                                                    | 134        |
| 15.4.      | Rituximab (anti-CD20) .....                                                     | 135        |
| 15.5.      | Drugs that stimulate platelet production .....                                  | 136        |
| 15.6.      | Conclusion .....                                                                | 137        |
| <b>16.</b> | <b>Mechanism of action of high dose intravenous immunoglobulin in ITP</b> ..... | <b>141</b> |
| 16.1.      | Introduction .....                                                              | 141        |
| 16.2.      | Mononuclear phagocyte system (MPS) blockade .....                               | 142        |
| 16.3.      | Anti-idiotype antibodies .....                                                  | 144        |
| 16.4.      | IgG Fc region sialylation and the inhibitory Fc receptor (FcγRIIB) .....        | 145        |
| 16.5.      | Cytokine modulation .....                                                       | 146        |
| 16.6.      | Neonatal Fc receptor (FcRn) .....                                               | 147        |
| 16.7.      | Dendritic cells (DCs) and immunomodulation .....                                | 148        |
| 16.8.      | Current and emerging IVIg alternatives and mimetics for use in ITP .....        | 149        |
| 16.9.      | Other mechanisms and conclusions .....                                          | 151        |
| <b>17.</b> | <b>Immune thrombocytopenia – the patients' perspective</b> .....                | <b>158</b> |
| 17.1.      | Patients "hate steroids" .....                                                  | 158        |
| 17.2.      | Rituximab .....                                                                 | 159        |
| 17.3.      | Patients try to avoid splenectomy .....                                         | 159        |
| 17.4.      | Patients and Thrombopoietin-Receptor Agonists (TRAs) .....                      | 159        |

|       |                                      |     |
|-------|--------------------------------------|-----|
| 17.5. | Other therapies.....                 | 160 |
| 17.6. | The quagmire of modern medicine..... | 160 |
| 17.7. | What patients really want.....       | 162 |
| 17.8. | Conclusions.....                     | 162 |

## **Quality of Life as a treatment endpoint for patients with ITP** **164**

|         |                                                          |     |
|---------|----------------------------------------------------------|-----|
| 18.1.   | Introduction.....                                        | 164 |
| 18.2.   | Assessment of Health Related Quality of Life in ITP..... | 164 |
| 18.2.1. | HRQoL in Adults.....                                     | 164 |
| 18.2.2. | HRQoL in Children.....                                   | 165 |
| 18.3.   | ITP symptoms in HRQoL.....                               | 165 |
| 18.3.1. | Bleeding and Bruising.....                               | 166 |
| 18.3.2. | Fatigue.....                                             | 167 |
| 18.4.   | Impact of treatments on HRQoL.....                       | 167 |
| 18.4.1. | First-line agents.....                                   | 167 |
| 18.4.2. | Second-line therapies.....                               | 168 |
| 18.5.   | Conclusion.....                                          | 169 |

## **Fatigue as a treatment end point in ITP** **172**

|       |                                                    |     |
|-------|----------------------------------------------------|-----|
| 19.1. | How do we define fatigue.....                      | 172 |
| 19.2. | How can we assess fatigue.....                     | 172 |
| 19.3. | How much of a problem is fatigue in ITP.....       | 173 |
| 19.4. | Why does fatigue develop in ITP.....               | 176 |
| 19.5. | Cytokines and Immune dysregulation.....            | 177 |
| 19.6. | How do we manage the ITP patient with fatigue..... | 179 |
| 19.7. | Improving the Standard of Care.....                | 180 |
| 19.8. | Conclusion.....                                    | 181 |

## **Guidelines for using ITP management guidelines** **186**

|       |                                                     |     |
|-------|-----------------------------------------------------|-----|
| 20.1. | Guidelines for management of ITP.....               | 187 |
| 20.2. | Pros and cons of guidelines.....                    | 187 |
| 20.3. | Evidence based vs. patient centered management..... | 188 |

## **State of the Art and future Considerations of ITP** **190**

|       |                                                                                            |     |
|-------|--------------------------------------------------------------------------------------------|-----|
| 21.1. | Heterogeneity of ITP.....                                                                  | 190 |
| 21.2. | Unknown etiology of ITP.....                                                               | 192 |
| 21.3. | Immunomodulation in inflammatory and autoimmune disorders.....                             | 192 |
| 21.4. | Platelet stimulation by thrombopoietin receptor agonists (TPO-RA) of megakaryopoiesis..... | 193 |
| 21.5. | Future progress and the question of adequate management of ITP.....                        | 194 |

## **List of abbreviations** **201**

## **Index** **203**