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109/litre). Therapies

SECTION 22 Haematological disorders 5240 include (1) low-dose aspirin—should be considered in patients with platelet counts less than 1000 × 109/litre and without evidence of acquired von Willebrand's disease; and (2) cytoreduction— hydroxycarbamide effectively reduces platelet counts and throm- botic episodes in high-risk patients; interferon-α, anagrelide, and other agents are also used. Prognosis—most patients will survive more than 10 years from diagnosis. Most deaths result from thrombotic complications. Introduction Thrombocytosis refers to a platelet count elevated above the ac- cepted normal range (>450 × 109/litre). The widespread use of auto- mated cell counters has made the identification of platelet count abnormalities a relatively common event. The clinical consequences of elevated platelet counts are usually determined by the cause of the thrombocytosis, ranging from the uneventful recognition of a laboratory abnormality, to medical emergencies such as life- threatening thrombosis or haemorrhage. Normal megakaryocytopoiesis An understanding of disorders of platelet production requires knowledge of the regulatory events that occur during normal megakaryocytopoiesis. Megakaryocyte development is a complex process in which a wide variety of regulatory signals work in con- cert to direct a highly specific response to thrombopoietic demand. A large number of cytokines including interleukins (IL-3, IL-6, and IL-11), stem cell factor, granulocyte–macrophage colony-stimulating factor, thrombopoietin, and, possibly, erythropoietin have been shown to stimulate megakaryocyte development. Thrombopoietin and the thrombopoietin receptor (MPL) are the primary physio- logical regulators of in vivo megakaryocytopoiesis. Thrombopoietin is produced primarily by the liver, but its mRNA has also been found in the kidney, muscle, and bone marrow. Thrombopoietin acts at dif- ferent levels of megakaryocyte maturation ranging from the prolif- eration and survival of haematopoietic stem cells/progenitor cells to megakaryocyte maturation, but does not significantly affect the release of platelets from megakaryocytes; thrombopoietin levels are regulated by the total mass of platelets and megakaryocytes, and thrombopoietin is cleared by binding to receptors on the surface of these cells. Like erythropoietin, thrombopoietin uses the JAK– STAT signalling pathway (see Chapter 22.3.5). Activation of the re- ceptor MPL by thrombopoietin provokes a conformational change of the JAK2 tyrosine kinase, phosphorylation of intracytoplasmic residues, and downstream activation of the genes controlling cell cycle status, differentiation, and apoptosis. A mutation in the 617 position of the JAK2 protein replacing the amino acid phenylalanine with valine disrupts the autoinhibitory domain of JAK2 and renders the kinase constitutively active. This mutation, JAK2 V617F, is pre- sent in the vast majority of patients with polycythaemia vera and in approximately 50% of patients with essential thrombocythaemia. Additional mutations found in essential thrombocythaemia include activating mutations in MPL and CALR. Gain-of-function deletions or insertional mutations of CALR exon 9 result in a mutant CALR protein preferentially associating with MPL that is bound to JAK2, which drives its phosphorylation. During times of thrombopoietic stress, there is increased pro- duction of thrombopoietin by the spleen and bone marrow. Inappropriately elevated levels of thrombopoietin may be observed in essential thrombocythaemia. This is probably not due to exces- sive production but rather impaired thrombopoietin clearance as- sociated with decreased expression of the thrombopoietin receptor by megakaryocytes and platelets. Molecular abnormalities in the thrombopoietin gene, however, have been identified in several fam- ilies with an autosomal dominant form of hereditary thrombocytosis where serum thrombopoietin levels are significantly elevated. This syndrome has been shown to be due to a mutation in a portion of the thrombopoietin gene, which plays a crucial role in regulating its expression. Pathophysiology and classification of thrombocytosis

Thrombocytosis can occur in response to many underlying clinical conditions (secondary or reactive), or as a consequence of a pri- mary abnormality in bone marrow function (primary). A classifi- cation of the causes of thrombocytosis is provided in Box 22.3.6.1. Reactive or secondary thrombocytosis accounts for over 80% of all recognized cases of thrombocytosis, iron deficiency being the most common cause. Short-lived, secondary thrombocytosis may be ob- served in situations such as trauma, acute bleeding, major surgery, or after strenuous physical exercise. Longer-term thrombocytosis Box 22.3.6.1 Classification of the causes of thrombocytosis • Autosomal dominant familial thrombocytosis • Secondary thrombocytosis (reactive):

— Iron deficiency

— Infection

— Postsplenectomy (or hyposplenism)

— Malignancy

— Trauma

— Inflammation (noninfectious)

— Blood loss

— Major surgery

— Exercise

— Rebound from myelosuppression • Primary thrombocytosis (nonreactive):

— Essential thrombocythaemia

— Chronic myeloid leukaemia

— Polycythaemia vera

— Primary myelofibrosis

— Unclassified myeloproliferative neoplasms

— Myelodysplastic syndromes

— Refractory anaemia with ringed sideroblasts and thrombocytosis (RARS-T) • Uncertain aetiology Adapted from The American Journal of Medicine, Vol. 96, Buss DH, et al., Occurrence, etiology, and clinical significance of extreme thrombocytosis: A study of 280 cases, Pages 247–53, Copyright © 1994, with permission from Elsevier.

22.3.6 Thrombocytosis and essential thrombocythaemia 5241 is associated with the presence of chronic disorders such as malig- nancy, inflammation, chronic infections, and iron deficiency an-

aemia. The pathophysiology underlying reactive thrombocytosis is not fully understood, but probably involves the increased generation of inflammatory cytokines such as IL-6, which appear to mediate in- creased transcription of thrombopoietin by the liver. Primary thrombocytosis by contrast is associated with a group of bone marrow disorders including chronic myeloid leukaemia, essential thrombocythaemia, polycythaemia vera, primary myelofibrosis, and the myelodysplastic syndromes. The level of ele- vation of platelet numbers is not helpful in differentiating a reactive from a primary process. An abnormality of thrombopoietin production or of the thrombopoietin receptor has been suggested as the basis of sev- eral familial disorders associated with thrombocytosis. In several families, a point mutation of the thrombopoietin gene leads to overproduction of thrombopoietin resulting in elevated levels of thrombopoietin and thrombocytosis. Patients with this autosomal dominant form of familial thrombocytosis have a benign course which is not complicated by thrombosis or haemorrhage or the de- velopment of acute leukaemia or myelofibrosis. A second familial form of thrombocytosis has been attributed to a mutation in the transmembrane mutation of MPL leading to its constitutive activa- tion. These familial forms of thrombocytosis are the consequence of germ-line mutations while the myeloproliferative neoplasms are the consequence of acquired somatic mutations. A third familial form of thrombocytosis has been described with germline JAK2 mutations; some, but not all, of these mutations not only result in thrombocytosis but additionally result in vascular events. Lastly, gelsolin, which is a protein involved in actin assembly and disas- sembly, is currently being evaluated as another familial cause of iso- lated thrombocytosis; the mechanism by which a mutation in this gene results in thrombocytosis is unknown. For the most part, the underlying medical disorder leading to re- active thrombocytosis can be identified by clinical criteria.

A number of laboratory tests can be useful in distinguishing primary from sec- ondary thrombocytosis. C-reactive protein synthesis in the liver is mediated by IL-6, with C-reactive protein levels being high in those patients with elevated IL-6 levels. Elevated levels of both IL-6 and C-reactive protein are strongly indicative of the elevated platelet count being reactive in origin. Cytogenetic analyses and use of the poly- merase chain reaction for the BCR-ABL1 translocation are useful to exclude the presence of a Philadelphia chromosome and a diagnosis of chronic myeloid leukaemia in a patient with thrombocytosis. Assays using probes for restriction fragment polymorphisms of genes located on the X chromosome are helpful in identifying clonal haematopoiesis in females with thrombocytosis. Clonal haemato- poiesis occurs in patients with myeloid malignancies such as essen- tial thrombocythaemia but not in cells of patients with secondary forms of thrombocytosis. More recently, the presence or absence of the JAK2 V617F mutation, calreticulin mutations, and/or MPL mutations (MPL W515L, MPL W515K, and MPL W515N) have been used to differentiate secondary cases of thrombocytosis from a Philadelphia-negative myeloproliferative neoplasm leading to ele- vated platelet numbers. The presence of these mutations in a patient with thrombocytosis is diagnostic of a myeloproliferative neoplasm. The natural history and prognosis of reactive thrombocytosis is defined by its underlying cause. The thrombocytosis per se is probably inconsequential and does not require specific therapy; it usually resolves after the treatment of the underlying cause. In con- trast, the thrombocytosis due to underlying myeloproliferative neo- plasm can cause life-threatening thromboembolic phenomena and bleeding episodes, and frequently requires specific cytoreductive therapy, emphasizing the need for accurate recognition. Essential thrombocythaemia Essential thrombocythaemia is a chronic myeloproliferative neo- plasm characterized by marked bone marrow megakaryocytic hyperplasia and peripheral blood thrombocytosis. The clinical course is punctuated by episodes of thrombosis and/or bleeding. In 1951, Dameshek suggested that essential thrombocythaemia

represented a myeloproliferative disease. The myeloproliferative neoplasms are currently thought to represent malignant stem cell disorders. Aetiology and pathogenesis The causative factors which lead to essential thrombocythaemia have become increasingly better understood. Its pathogenesis in- volves the abnormal proliferation of a blood cell precursor that differentiates mainly towards the megakaryocytic/platelet lineage. Current evidence suggests that hypersensitivity to stimulatory cytokines such as thrombopoietin might provoke the expansion of the megakaryocytic progenitor pool. The clonal origin of haem- atopoiesis in patients with myeloproliferative neoplasms was ini- tially established through biochemical isoenzyme characterization of the blood cells of affected women who were heterozygous for glucose-6-phosphate dehydrogenase. Analysis of X-linked re- striction fragment length polymorphisms in affected women has confirmed a clonal pattern in some cases. There are, however, a significant number of patients with polyclonal myelopoiesis. These nonclonal cases may have a decreased risk for thrombosis. The finding of the JAK2 V617F mutation in Philadelphia chromosome- negative myeloproliferative neoplasms has provided new insight into the pathogenesis of this disease. Approximately 50% of pa- tients with essential thrombocythaemia are JAK2 V617F positive. The patients who are positive for the mutation almost uniformly have a low burden of JAK2 V617F (<50%) as compared with poly- cythaemia vera. Essential thrombocythaemia patients with a high allele burden are older, have more symptoms (especially aquagenic pruritus), a larger spleen volume, and significantly higher rate of cardiovascular complications. Although polycythaemia vera pa- tients almost always have haematopoietic progenitors that are homozygous for the JAK2 V617F mutation, such homozygous pro- genitor cells are only occasionally observed in essential thrombo-cythaemia patients. These data indicate that the homologous recombination step which leads to mutational homozygosity in polycythaemia vera rarely occurs in essential thrombocythaemia. Furthermore, the degree of mutant allelic chimerism remains constant over time. Patients with JAK2 V617F-positive essential thrombocythaemia have a higher haematocrit, higher white blood cell count, and higher rate of transformation to polycythaemia vera than patients who are JAK2 V617F-negative. These findings have led some investigators to suggest that JAK2 V617F-positive essen- tial thrombocythaemia represents a forme fruste of polycythaemia

 vera. Acquired mutations of the thrombopoietin receptor MPL at position 515 have been observed in 4 to 5% of patients with es- sential thrombocythaemia and 9% of patients with JAK2 V617F- negative essential thrombocythaemia. A number of patients have been shown to possess both the MPL and JAK2 V617F mutations. Although the MPL mutations were first observed in patients with primary myelofibrosis, they are now known to also occur in pa- tients with essential thrombocythaemia. MPL mutant-positive patients have lower haemoglobin levels but higher platelet counts than essential thrombocythaemia patients who do not have this mutation. More recently, CALR mutations have been described in about 30 to 40% of patients with essential thrombocythaemia. The normal function of calreticulin is to ensure appropriate binding of newly synthesized glycoproteins within the endoplasmic re- ticulum and regular calcium homeostasis. Over 50 types of mu- tations have been observed in essential thrombocythaemia and primary myelofibrosis, which result in calreticulin losing its calcium-binding and endoplasmic reticulin retention domains. The resultant mutant protein interacts directly with MPL, keeping it active and thereby activating a downstream JAK–STAT pathway. Two primary types of CALR mutations have been described. Type 1 mutations account for 65% of those observed and are charac- terized by a 52-bp deletion while type 2 mutations account for 32% and are characterized by 5-bp insertion. The remaining mu- tations are

referred to as type 3, and account for the remaining 3%. Patients with type 1 mutations are associated with a higher risk of myelofibrotic transformation while type 2 mutations have a more indolent course as well as a lower risk of thrombosis despite very high platelet counts. CALR mutations are not typically found in patients with MPL or JAK2 mutations. Together these three mutations account for over 90% of essential thrombocythaemia cases. However, in 10% of essential thrombocythaemia, the driver mutation is currently unknown and these patients are referred to as ‘triple negative’. Recently the disease-causing mutations in such triple-negative cases have been examined using whole-exome sequencing. Noncanonical mutations of MPL and JAK2, outside of the exons usually examined for diagnostic purposes, were present in 18.9% of cases. All the newly identified JAK2 mutations lead to constitu- tive activation of the JAK–STAT signalling pathway. The inability to detect mutations in the remainder of such triple-negative patients could be due to the technical limitations of the whole-exome sequencing or the possibility that such individuals have a heredi- tary form of thrombocytosis. A recent study of essential thrombocythaemia patients in a paediatric population revealed that haematopoiesis was more often polyclonal and JAK2 V617F-negative. As compared with the adult population, about 20% of such paediatric cases had monoclonal haematopoiesis and JAK2 V617F positivity was significantly less frequent than in adults (20% vs 50–60%). CALR exon 9 mutations are observed in an additional 10% of patients less than 18 years of age. Although one may hypothesize that clonal haematopoiesis in nonclonal essential thrombocythaemia patients may become more apparent with age, no significant evidence has been provided so far to support the transition from nonclonal to clonal haematopoiesis. Furthermore, patients who are negative for JAK2 V617F or MPL mutations at presentation have not been observed to acquire the mutation over time. Epidemiology The true incidence of essential thrombocythaemia is unknown due to the lack of large epidemiological studies. Several smaller studies estimated the incidence of essential thrombocythaemia to be 1.5 to 2.4 patients per 100 000 population annually. Approximately 6000 new cases are identified each year in the United States of America. There seems to be a slight female predominance and the usual age at onset is between 50 and 60 years. Approximately 20% of all cases occur in individuals younger than 40 years, but it is very rarely seen during childhood. Pathobiology The characteristic clinical features are dominated by the thrombo cytosis and abnormalities in platelet function. The association be- tween increased numbers of circulating platelets and ischaemic episodes remains unclear, but the duration of thrombocytosis may play a role. Microvascular thrombosis results in a variety of clinical syndromes associated with digital and cerebrovascular ischaemia. Abnormalities in platelet function occur in 35 to 100% of patients, and prolongation of the bleeding time occurs in 7 to 19%. Despite being common, these abnormalities are poor predictors of bleeding and/or thrombotic risk. This is in contrast to the acquired von Willebrand’s disease and erythromelalgia, clinical entities not in- frequently seen in association with essential thrombocythaemia. In acquired von Willebrand’s disease, extreme thrombocytosis (>1000 × 109/litre) induces the adsorption of larger von Willebrand’s multimers on to platelet membranes, with their subsequent degrad- ation, triggering a haemostatic defect quite similar to that observed in type 2 von Willebrand’s disease. Erythromelalgia occurs commonly in patients with essential thrombocythaemia. Erythromelalgia refers to a syndrome charac- terized by redness and burning pain in the extremities which results from platelet-mediated thrombosis of the arterial microvasculature. If left untreated it may progress to frank gangrene. The exquisite platelet response to cyclooxygenase inhibitors such as aspirin and indomethacin suggests that prostaglandin endoperoxides produced by the metabolism of arachidonic acid might play a major role in the generation of platelet-associated thrombosis. Increased frequency of venous thrombosis in uncommon sites such as the splanchnic vasculature

leading to catastrophic intra- abdominal thromboses such as Budd–Chiari syndrome have recently been reported in JAK2 V617F-positive patients who sub- sequently go on to develop essential thrombocythaemia. Although the increased thrombotic risk cannot be explained exclusively by the presence of the JAK2 V617F mutation, it appears to contribute to the increased risk of thrombosis in these patients. Clinical manifestations As many as two-thirds of patients with essential thrombocythaemia are asymptomatic at diagnosis. Most symptomatic patients pre- sent with either a thrombotic episode or a minor bleeding episode. Bleeding can occur spontaneously but is frequently associated with the recent use of a nonsteroidal anti-inflammatory drug (NSAID). Common sites of haemorrhage include the gastrointestinal and the genitourinary tracts; there is also easy bruising. Thrombosis leads to the most common presenting symptoms and can occur in arteries and veins, large or small. Occlusion of the splanchnic vessels and of

 the superficial and deep veins of the lower extremities is common. Pulmonary emboli may also occur. An occasional patient presents with thrombosis of the hepatic veins causing the Budd–Chiari syn- drome or with occlusion of the renal veins manifesting clinically as nephrotic syndrome. When the microcirculation is involved, a number of clinical syn- dromes may occur. Palpable lesions with small areas of gangrene indistinguishable from vasculitic lesions of rheumatoid arthritis or systemic lupus erythematosus may be observed. Erythromelalgia may occur in association with transient ischaemic attacks or acute episodes of cardiac angina. Peripheral pulses are usually preserved; this helps differentiate erythromelalgia from atherosclerotic-related ischaemia. Neurological symptoms are common and include headaches and paraesthesias of the extremities. Transient ischaemic attacks may present with symptoms of unsteadiness, dysarthria, dysphoria, motor hemiparesis, scintillating scotomas, amaurosis fugax, vertigo, dizziness, migraine headaches, and seizures. On occasion, transient ischaemic attacks may progress to established infarcts. Myocardial ischaemia with normal angiograms occurs occasion- ally. Splenic enlargement is observed in 40 to 50% of individuals and 20% have hepatic enlargement. Laboratory evaluation An elevated platelet count, often above 450 to 1000 × 109/litre, is characteristic. The absolute number of platelets, even if higher than 1000 × 109/litre, is not diagnostic of essential thrombocythaemia, as extreme elevations in platelet numbers may be observed in reactive thrombocytosis. Marked changes in platelet morphology, which include large and bizarre-looking platelets sometimes forming ag- gregates, are also characteristic and may be more useful in helping distinguishing primary from reactive thrombocytosis. The bone marrow is hypercellular with megakaryocytic hyperplasia. Clusters of hyperlobulated megakaryocytes are often observed within the marrow. Absent or diminished iron stores are seen frequently. This may be an epiphenomenon of an underlying myeloproliferative neo- plasm or a true expression of iron depletion in patients with chronic bleeding. Reticulin fibrosis is present in one-quarter of bone marrow specimens but collagen is limited. Mild leucocytosis is common. Molecular analysis for JAK2 V617F, CALR, and MPL muta- tions is an important diagnostic tool in identifying patients with myeloproliferative neoplasms. If thrombocytosis associated with megakaryocytic hyperplasia, and a JAK2 V617F, CALR, or MPL mutation is observed in the absence of the clinical or laboratory features of one of the other myeloproliferative neoplasms such as polycythaemia vera or primary myelofibrosis, a diagnosis of es- sential thrombocythaemia is certain. Unfortunately, for the other 10% of the patients with essential thrombocythaemia who lack the above-mentioned mutations the diagnosis remains one of exclusion, although haematopoietic cell clonality assays are frequently useful in women. Such patients who are thought to have essential thrombo- cythaemia based upon marrow histopathology in the absence of the formerly

mentioned three mutations are referred to as triple- negative essential thrombocythaemia. Platelet function abnormalities are commonly found and include defective platelet aggregation in response to adrenaline, ADP, and col- lagen. Aggregation in response to arachidonic acid and ristocetin is often normal. An acquired platelet storage pool disease also occurs due to abnormalities in the content and release of α granules associated with a state of increased platelet activation. Cytogenetic evidence for a Philadelphia chromosome and/or the molecular identification of the BCR-ABL1 fusion gene aids in distinguishing essential thrombocyth- aemia from chronic myeloid leukaemia. The presence of dyspoietic changes in bone marrow precursor cells and of characteristic chromo- somal abnormalities suggests the diagnosis of myelodysplasia. In par- ticular, the 5q– syndrome is associated with thrombocytosis. More recently, mutations in splicing genes (e.g. SF3B1) have been described in refractory anaemia with ringed sideroblasts and thrombocytosis (RARS-T), which has features of both a myelodysplastic syndrome and myeloproliferative neoplasm and is classified as such in the World Health Organization (WHO) classification. The diagnostic criteria and management of the other myeloproliferative neoplasms associated with thrombocytosis are outlined in other chapters. Distinguishing essential thrombocythaemia from prefibrotic primary myelofibrosis can be challenging; the presence of an elevated lactate dehydrogenase, systemic symptoms, leucocytosis, or a leucoerythroblastic smear with minimal fibrosis on bone marrow biopsy still may suggest prefibrotic primary myelofibrosis rather than essential thrombocythaemia des- pite the presence of thrombocytosis. Careful consideration of the diag- nostic features by WHO criteria between essential thrombocythaemia and prefibrotic myelofibrosis is important from a prognostic stand- point, as retrospective data suggest the latter have a reduced survival associated with increased risk for evolution to overt myelofibrosis and acute leukaemia. Cytogenetic abnormalities occur in approxi- mately 5% of patients with essential thrombocythaemia, and the most common are 1q–, 20q–, 21q–, and 1q+. Elevated vitamin B12 levels occur in 25% of patients. Diagnostic criteria and differential diagnosis The revised WHO diagnostic criteria for essential thrombocyth- aemia are given in Box 22.3.6.2. Essential thrombocythaemia was Box 22.3.6.2 2016 WHO criteria for the diagnosis of essential thrombocythaemia Major criteria 1 Platelet count of at least 450 × 109/litre. 2 Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. There should be no sig- nificant increase or left shift in neutrophil granulopoiesis or erythro- poiesis and very rarely minor (grade 1) increase in reticulin fibres. 3 Not meeting WHO criteria for chronic myeloid leukaemia, polycy- thaemia vera, primary myelofibrosis, myelodysplastic syndrome, or other myeloid neoplasm. 4 Demonstration of JAK2 V617F, CALR, or MPL mutations or other clonal marker. Minor criterion 1 Presence of another clonal marker or absence of evidence for reactive thrombocytosis. Diagnosis of essential thrombocythaemia requires all four of the following major criteria or presence of the first three major criteria and the one minor criterion Source data from Arber DA, et al. (2016). The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood, 127, 2391–405.

 previously a diagnosis of exclusion, but the advent of JAK2 V617F, CALR, and MPL mutational analyses have greatly facilitated the diagnosis in approximately 90% of cases. The presence of these mu- tations in the setting of thrombocytosis without evidence of polycy- thaemia vera is virtually diagnostic of essential thrombocythaemia. These diagnostic criteria are, however, of less use in paediatric pa- tients since many of these individuals are JAK2 V617F negative. Thrombocytosis may be the consequence of primary bone

marrow disorders associated with increased platelet production (nonreactive thrombocytosis), or a secondary response to an underlying disorder (reactive thrombocytosis). Box 22.3.6.1 summarizes the most im- portant causes of thrombocytosis: iron deficiency anaemia, infec- tion/inflammation, malignancy, trauma, and hyposplenism, are the most commonly encountered disorders. The exclusion of an iden- tifiable cause for reactive thrombocytosis, in particular iron defi- ciency, is a necessary step. Risk assessment Essential thrombocythaemia is a heterogeneous disorder asso- ciated with patients encountering a varied risk of developing life- threatening complications. Many patients enjoy survival fairly similar to that of their unaffected peers but a subset of patients is at a high risk of developing additional thromboses. Myelosuppressive therapy should be reserved for patients at a high risk of developing such thrombotic complications. A risk-based decision approach to therapy is outlined in Table 22.3.6.1 to identify such patients. Advanced age (≥60 years) and a previous history of thrombosis clearly define a group at high risk for the development of life- threatening complications. The degree of thrombocytosis and the presence of associated cardiovascular risk factors, particu- larly smoking and obesity, are also taken into consideration when making treatment decisions. The International Prognostic Score for Thrombosis in Essential Thrombocythemia (IPSET) uses patient age, thrombosis history, and cardiovascular risk factors but addition- ally recognizes that the presence of a JAK2 V617F mutation predis- poses additional thrombotic risk. The utility of this scoring system to guide treatment decisions is unknown at this time since it has not been validated in a prospective fashion. In addition, it does not predict the risk for evolution to myelofibrosis or acute leukaemia. Isolated thrombocytosis per se is not an indication for therapy; how- ever, it is common practice to treat extreme thrombocytosis (platelet count >1500 × 109/litre) because of the increased risk of bleeding rather than thrombotic complications. The use of CALR, JAK2, or MPL mutation status is not currently incorporated into risk assess- ment for therapeutic decision although increasing data suggest that these are distinct clinicopathological entities. Treatment The present goal of therapy in essential thrombocythaemia is to con- trol symptoms and prevent thrombotic and haemorrhagic compli- cations. Should a decision be made to treat the patient based on risk assessment, the platelet count should be reduced to 400 × 109/litre. Although no target platelet count has been determined to be optimal to reduce the incidence of thrombotic episodes in rigorous clinical trials, this is considered a safe level by most practising physicians in the field. A number of agents are effective in the treatment of essential thrombocythaemia. Low-dose aspirin (81–100 mg/day) has been shown to be safe and may decrease the recurrence of microcirculatory events (erythromelalgia/transient ischaemic attacks) and prevent the development of other thrombotic phenomena, especially in combin- ation with myelosuppressive agents in high-risk patients. In order to minimize the risk of iatrogenic bleeding, only patients with platelet counts less than 1500 × 109/litre and without evidence of an acquired von Willebrand’s disease should be considered for low-dose aspirin administration. The use of hydroxycarbamide, an antimetabolite that interferes with DNA repair, decreased the number of thrombotic events in a randomized study of high-risk patients when given at 15 mg/kg ini- tially, with subsequent adjustments based on initial response. In this study, the target was a platelet count of less than 600 × 109/litre. It is unknown whether tighter control (<350–400 × 109/litre) is more effective in reducing thrombotic and haemorrhagic complications. The onset of action is usually 3 to 5 days and frequent side effects include dose-related neutropenia, nausea, stomatitis, hyperpigmen- tation, rash, nail changes, leg ulcers, increased risk of squamous cell carcinoma of the skin, and hair loss. The leukaemogenic potential of hydroxycarbamide when given as a single agent is still a subject of controversy although it is clearly less leukaemogenic than alkylating agents. Recent data from at least two large studies, one in polycy- thaemia vera and the other one

in essential thrombocythaemia pa- tients, failed to show an increased incidence of acute leukaemia in patients treated with hydroxycarbamide. Interferon-α, a biological response modifier, is also useful in treating patients with essential thrombocythaemia. Ninety per cent response rates with median times to response of approximately 3 months have been seen when 3 to 5 million units are admin- istered subcutaneously 3 to 5 days per week. It is nonmutagenic and does not cross the placenta. Frequent side effects include influenza-like symptoms, fatigue, lethargy, and depression. The long-term use of interferon is associated with mild weight loss, alopecia, autoimmune thyroiditis, autoimmune haemolytic an- aemia, and neuropsychiatric effects. Its extensive toxicity profile and the need for parenteral administration limit its use as initial therapy, particularly in elderly patients. Pegylated forms of inter- feron have a prolonged half-life, can be administered weekly, and are often better tolerated. Prolonged therapy with interferon has the potential to reduce the allele burden of the patient's driver mutation (CALR, JAK2 V167F, or MPL) and in 20 to 30% of pa- tients to result in a complete molecular remission. In addition, a subset of patients clear the marker chromosomal abnormal- ities associated with their disease. It remains unknown whether the correction of these molecular correlates translate into im- proved survival, decreased thrombotic events, or progression to myelofibrosis or acute leukaemia. Many patients find it difficult to continue to receive interferon for more than 1 to 2 years primarily due to adverse events. Anagrelide is another treatment option for patients with essen- tial thrombocythaemia. This drug acts by selectively inhibiting megakaryocytic maturation. Responses have been documented in over 90% of treated patients with a median time to response of 2.5 to 4 weeks and an onset of action of 6 to 10 days. Anagrelide is nonmutagenic and its use has not been associated with the de- velopment of acute leukaemia. The UKMRC PT-1 study com- paring hydroxycarbamide with anagrelide in addition to aspirin therapy found that patients treated with anagrelide plus aspirin

 had an increased rate of arterial thrombotic events, haemor- rhage, and transformation to myelofibrosis as compared to the hydroxycarbamide plus aspirin arm. There was no increase in the incidence of acute leukaemia in the hydroxycarbamide arm. On the other hand, the ANAHYDRET study demonstrated that anagrelide was not inferior to hydroxycarbamide in the prevention of throm- botic complications in patients with essential thrombocythaemia and its use was not associated with an increase in transformation to acute leukaemia or myelofibrosis. Anagrelide is a good second- line treatment option for patients intolerant to hydroxycarbamide. Common side effects of anagrelide therapy include headaches, diz- ziness, fluid retention, palpitations, nausea, abdominal pain, and diarrhoea. Anagrelide can trigger episodes of tachyarrhythmias and heart failure, especially in the elderly. For this reason, it should be used carefully in older people and avoided in patients with known heart disease. Alkylating agents have been extensively used in the past to treat essential thrombocythaemia. Within this group of agents, melphalan has been shown to be quite effective and relatively nontoxic, with predictable cytopenias as its major untoward effect. The drug is useful in treating the very elderly or those with com- pliance issues. It is usually prescribed at 4 mg/day until a platelet count of 400 × 109/litre is reached. Therapy can then be stopped and patients experience prolonged periods of normalization of platelet numbers. Additional courses can be given if and when the platelet count rises over 400 × 109/litre. Given the number of available therapeutic options and their dif- ferent toxicity profiles, the choice of the appropriate cytoreductive drug for a given individual requires the consideration of a number of variables. These include age, childbearing potential, projected life expectancy, comorbidities, and cost of treatment. Furthermore, the overall low risk for the development of life-threatening com- plications that affect

patients with essential thrombocythaemia highlights the need for systematic, risk-based approaches to thera- peutic decision-making (Table 22.3.6.1). All patients should stop smoking. Indiscriminate use of high doses of NSAIDs should be avoided; their excessive use is clearly associated with bleeding episodes. Low-risk patients have a risk of thrombosis similar to that of an age- and sex-matched control population and a very low risk of life- threatening bleeding. These observations support close observa- tion without cytoreductive therapy as the most sensible approach. Although the use of aspirin therapy is common in this group, retro- spective studies have failed to show a benefit. High-risk patients are those more than 60 years of age and with a prior history of throm- bosis. According to the results presented in the PT-1 trial, these pa- tients should be treated with hydroxycarbamide as the cytoreductive agent of choice, in addition to aspirin. Anagrelide or a pegylated form of interferon should be offered to patients who are intolerant of hydroxycarbamide or who have developed adverse effects to it. For elderly patients with limited projected survival (<10 years) and who either have problems with drug compliance or are too ill to comply with the minimum follow-up requirements during cytoreductive therapy, intermittent melphalan might be appropriate. α-Interferon may be an acceptable option in younger patients of reproductive age with a history of life-threatening thrombotic episode. In pa- tients at intermediate risk based on platelet numbers at or greater than 1000 to 1500 × 109/litre and/or patients who have acquired von Willebrand’s disease, platelet reduction therapy is indicated to avoid the higher risk of complications. Smokers and obese individuals, unless symptomatic, should be managed by risk modification. Smoking has been proved to be an in- dependent risk factor for developing arterial thrombotic complica- tions. Patients with essential thrombocytopenia should be strongly encouraged to stop smoking to decrease their thromboembolic risk. In severe, life-threatening episodes, rapid cytoreduction may be achieved by plateletpheresis or by the administration of high doses of hydroxycarbamide. In patients who present with a life- threatening episode of acute bleeding, the site of bleeding should be promptly identified and any antiplatelet agent should be stopped. Those suffering from an acquired von Willebrand’s disease can be treated with desmopressin and von Willebrand’s factor concentrates. If the bleeding is due to a platelet function abnormality, or if alter- native haemostatic agents have failed, platelet transfusion therapy is recommended. Cytoreductive therapy with hydroxycarbamide must be promptly initiated. Up to 10% of patients with essential thrombocythaemia will evolve to secondary myelofibrosis, recognized by the development of cytopenias, leucoerythroblastic blood picture, and worsening splenomegaly. These patients have a very poor prognosis and should undergo evaluation for allogeneic stem cell transplantation. The use of reduced-intensity conditioning regimens for allogeneic stem cell transplantation has been shown recently to improve the outcome of such patients with a relatively low mortality rate. At this time, JAK inhibitors do not have a role in the treatment of essential thrombocythaemia. The management of patients who are or want to become pregnant requires special consideration. The risk of fetal loss is quite high (c.40%). High-risk pregnancy is defined as one occurring in an individual with a previous throm- bosis or major bleeding episode, platelet count more than 1500 × Table 22.3.6.1 Risk stratification-based treatment of essential thrombocythaemia Risk categorya Treatment Low risk Observation Age <60 years, and No history of thrombosis, and Platelet count <1000 × 109/litre, and No cardiovascular risk factors (smoking, obesity) High risk Treatment Age ≥60 years, or Previous history of thrombosis Intermediate risk Treatmentb Age <60 years, and Platelet count >1000–1500 × 109/litre, or Cardiovascular risk factors (smoking, obesity) a Leucocytosis and JAK2 V617F mutation appear to confer a higher risk of thrombosis, but no established treatment guidelines exist for these patients. b The decision to treat is at the discretion of the clinician. We offer

treatment to most of our patients with platelets more than 1000–1500 × 109/litre. Risk modification is strongly encouraged. Adapted from Blood Reviews, Vol. 19, Finazzi G, Barbui T, Risk-adapted therapy in essential thrombocythemia and polycythemia vera, Pages 243–52, Copyright © 2005, with permission from Elsevier.

 109/litre, and previous severe complications such as fetal loss or placental abruption. Patients with low or intermediate disease risk should be managed with careful observation. Specific treat- ment should be considered for high-risk pregnancies as follows. (1) If previous thrombosis or major complications during prior pregnancies have occurred, patients should receive low molecular weight heparin throughout pregnancy until 6 weeks postpartum. (2) If there is a history of major bleeding, or if the platelet count is above 1500 × 109/litre, aspirin should be avoided and consideration should be given to cytoreduction with interferon to decrease the platelet count to normal levels. Despite the lack of endorsement by the manufacturers of α-interferon, it is the drug of choice during pregnancy given its lack of mutagenic potential and its inability to cross the placenta. Hydroxycarbamide, given its mechanism of ac- tion, could theoretically cause fetal malformations, and anagrelide, because of its small molecular size, probably crosses the placenta and may cause life-threatening thrombocytopenia and haemor- rhage in the fetus. Despite these concerns, several reports have de- scribed first-trimester exposures to these two drugs resulting in the delivery of normal newborns. We therefore do not consider unintended exposures to hydroxycarbamide or anagrelide as ab- solute indications for the termination of a pregnancy. Recently, JAK2 V617F-positive essential thrombocythaemia has been found to be an independent adverse predictor of pregnancy outcome. These pregnancy-associated complications in patients with JAK2 mutations were not prevented by the use of aspirin therapy raising the question of whether prophylactic anticoagulant therapy is war- ranted for JAK2 V617F-positive patients. Prognosis The probability that a patient with essential thrombocythaemia will survive 10 years is 64 to 80%, not substantially different from that of a control age- and sex-matched population. The actual risk for the development of a catastrophic thrombotic or haemorrhagic event in an asymptomatic patient is quite low. Most deaths come from thrombotic complications. Transformation to myelofibrosis and/or acute leukaemia has been reported with increasing frequency at a rate of transformation of 3 to 10%. JAK2 V617F-positive essential thrombocythaemia not infrequently evolves into the clinical picture of polycythaemia vera. While the presence or absence of JAK2, MPL, or CALR muta- tions has an impact on prognosis in primary myelofibrosis, the im- pact in essential thrombocythaemia is less clear but evolving. Those with CALR mutations, including type 1 and 2 mutations, appear to have lower thrombotic risk than those with the JAK2 mutation. Type 1 CALR mutations have a higher risk of thrombosis as well as transformation to primary myelofibrosis than type 2 mutations. Type 1 CALR mutations also have a higher risk of transformation to primary myelofibrosis than those patients with JAK2 mutations, who appear to have a similar risk as those with type 2 mutations. For patients with MPL mutations, conflicting data exist regarding thrombotic risk. Overall survival may be inferior in those patients with MPL mutations and best in those with triple negative essen- tial thrombocythaemia while JAK2 and CALR mutations are inter- mediate. More recent analyses have suggested that mutational status does not impact upon overall survival or leukaemia-free survival. Therefore, more research is needed to clarify the clinical impact of these individual mutations. Future directions A better understanding of the factors that contribute to the devel- opment of thrombotic episodes and evolution to myelofibrosis in essential thrombocythaemia patients is clearly required. Studies that evaluate the effects of currently used therapeutic agents on patient outcomes are needed before conclusions can be made on when to treat with a particular agent. Since target platelet numbers

following treatment are not predictive of eliminating the risk of thrombosis, additional biomarkers are needed to guide the management of such patients. FURTHER READING Arber DA, et al. (2016). The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood, 127, 2391–405. Barbui T, Finazzi G (2007). Therapy for polycythemia vera and essen- tial thrombocythemia is driven by the cardiovascular risk. Semin Thromb Hemost, 33, 321–9. Barbui T, et al. (2011). Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol, 29, 761–70. Barbui T, et al. (2011). Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morpho- logic diagnosis: an international study. J Clin Oncol, 29, 3179–84. Barbui T, et al. (2013). Problems and pitfalls regarding WHO-defined diagnosis of early/prefibrotic primary myelofibrosis versus essential thrombocythemia. Leukemia, 27, 1953–8. Beer PA, et al. (2011). How I treat essential thrombocythemia. Blood, 117, 1472–82. Ding J, et al. (2004). Familial essential thrombocythemia associated with a dominant-positive activating mutation of the c-MPL gene, which encodes for the receptor for thrombopoietin. Blood, 103, 4198–200. Dingli D, Tefferi A (2005). A critical review of anagrelide therapy in essential thrombocythemia and related disorders. Leukemia Lymphoma, 46, 641–50. Elala YC, et al. (2016). Calreticulin variant stratified driver mutational status and prognosis in essential thrombocythemia. Am J Hematol, 91, 503–6. Elliott MA, Tefferi A (2005). Thrombosis and haemorrhage in polycy- thaemia vera and essential thrombocythaemia. Br J Haematol, 128, 275–90. Finazzi G, Barbui T (2005). Risk-adapted therapy in essential thrombo- cythemia and polycythemia vera. Blood Rev, 19, 243–52. Finazzi G, Harrison C (2006). Essential thrombocythemia. Semin Hematol, 42, 230–8. Fruchtman SM, Hoffman R (2005). Essential thrombocythemia. In: Hoffman R, et al. (eds) Hematology: basic principles and practice, pp. 1177–296. Churchill Livingstone, Philadelphia. Gisslinger H (2006). Update on diagnosis and management of essential thrombocythemia. Semin Thromb Hemost, 32, 430–6. Gisslinger H, et al. (2013). Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial. Blood, 121, 1720–8. Harrison C (2005). Pregnancy and its management in the Philadelphia negative myeloproliferative diseases. Br J Haematol, 129, 293–306. Harrison CN, et al. (2005). Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med, 353, 33–45.

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