RISK STRATIFICATION FOR THROMBOSIS IN MYELOPROLIFERATIVE DISORDERS

NOTE: Risk stratification models presented by other authors may vary.

	ESSENTIAL THROMBOCYTHEMIA	POLYCYTHEMIA VERA

LOW RISK	Age less than 40 years with all of the following:
	    NO prior thrombosis or hemorrhage
	    NO hypertension or diabetes
	    Platelet count $< 1500 \times 10^9$/L
	    NO familial thrombophilia/cardiovascular disease*
		Age less than 40 years with all of the following:
		    NO prior thrombosis or hemorrhage
		    NO congestive cardiac failure, hypertension or diabetes
		    NO familial thrombophilia/cardiovascular disease*
		    NO symptomatic or progressive splenomegaly

INTERMEDIATE RISK**	Age 40 – 60 years with all of the following:
	    NO prior thrombosis
	    NO hypertension or diabetes
	    Platelet count $< 1500 \times 10^9$/L
	        OR
	    Patients aged < 60 years and familial thrombophilia/cardiovascular disease*
		Age 40 – 60 years with all of the following
		    NO prior thrombosis
		    NO congestive cardiac failure, hypertension or diabetes
		    Platelet count $< 1500 \times 10^9$/L
		    NO progressive or symptomatic splenomegaly
		        OR
		    Patients aged < 60 years and familial thrombophilia/cardiovascular disease*

HIGH RISK**	Either age greater than 60 years OR with any *one* of the following:
	    Prior thrombosis or hemorrhage
	    Platelet count greater than 1000 – 1500 $\times 10^9$/L
	    Hypertension
	    Diabetes requiring treatment
		Either age greater than 60 years OR with any *one* of the following:
		    Prior thrombosis or hemorrhage
		    Platelet count greater than 1000–1500 $\times 10^9$/L
		    Congestive cardiac failure
		    Hypertension
		    Diabetes
		    Progressive or symptomatic splenomegaly

*The role of familial thrombophilia or cardiovascular disease in risk stratification is controversial.
**An intermediate risk category particularly for PV is controversial.
***Some risk stratification models do not put patients into a high risk group based on the presence of hypertension or diabetes.

Reference: Adapted from Harrison CN. Platelets and Thrombosis in Myeloproliferative Diseases. *Hematology Am Soc Hematol Educ Program* 2005:409 – 15.

TREATMENT RECOMMENDATIONS BASED ON THROMBOSIS RISK

NOTE: Treatment options presented by other authors may vary.

	ESSENTIAL THROMBOCYTHEMIA	POLYCYTHEMIA VERA
ALL PATIENTS	Seek and aggressively manage all reversible risk factors for vascular disease and determine family history. Aspirin 75 mg daily in the absence of active contraindications. For those patients with platelet count $> 1000 \times 10^9$/L it is wise to exclude acquired von Willebrand disease.	
LOW RISK	NO cytoreductive therapy	Phlebotomy to maintain Hct < 0.45**
INTERMEDIATE RISK	NO cytoreductive therapy	Phlebotomy to maintain Hct < 0.45**
HIGH RISK	Control platelet count to less than 400×10^9/L with: Hydroxyurea Consider interferon (IFN)$_\alpha$ or anagrelide for young patients (less than 40 years).	Control Hct < 0.45 and plt $< 400 \times 10^9$/L with: Hydroxyurea Consider IFN$_\alpha$ or anagrelide for young patients (less than 40 years).
REFRACTORY OR INTOLERANT	Change cytotoxic to one of low leukemogenic potential: Consider IFN$_\alpha$ or anagrelide If patient older than 75 years, consider busulfan or P^{32}	Change cytotoxic to one of low leukemogenic potential: Consider IFN$_\alpha$ or anagrelide If patient older than 75 years, consider busulfan or P^{32}

*Where possible, all low and intermediate risk group patients with either ET or PV should be entered into clinical trials
**For patients (particularly female) with on-going symptoms, a further reduction of Hct to < 0.42 is recommended but not supported by published evidence

Reference: Adapted from Harrison CN. Platelets and Thrombosis in Myeloproliferative Diseases. Hematology Am Soc Hematol Educ Program 2005:409 – 15.

BCR:ABL NEGATIVE MYELOPROLIFERATIVE DISORDERS

SEE ALSO MALIGNANT HEMATOLOGY SECTION

NOTE: PV = Polycythemia Vera, ET = Essential Thrombocytosis, MF = Myelofibrosis,
HES = Hypereosinophilic Syndrome

ANAGRELIDE

Anagrelide	0.5 mg	PO	BID–TID

Titrate dose at 1–2 week intervals until reaching desired effect.

References: Harrison CN, et al. *N Engl J Med* 2005;353:33 – 45 (ET); Storen EC and Tefferi A. *Blood* 2001;97:863 – 6 (ET); Steurer M, et al. *Cancer* 2004;101:2239 – 46 (ET and PV).

ASPIRIN – LOW DOSE ECASA

ECASA	75 – 100 mg	PO	Daily

References: Landolfi R, et al. *N Engl J Med* 2004;350:114 – 24 (PV); Jensen MK, et al. *Eur J Haematol* 2000;65:132 – 9 (ET).

HYDROXYUREA

Hydroxyurea	500 mg	PO	BID

Titrate dose at 1–2 week intervals until reaching desired effect.

References: Harrison CN, et al. *N Engl J Med* 2005;353:33 – 45 (ET); Kaplan ME, et al. *Semin Hematol* 1986;23:167 – 71 (PV); Lofvenberg E and Wahlin A. *Eur J Haematol* 1988;41:375 – 81 (PV, ET, and MF).

INTERFERON ALFA

Interferon alfa	$1 – 3 \times 10^6$ units/dose	SQ	3 times a week

Titrate dose at 1–2 week intervals until reaching desired effect.

References: Silver RT. *Cancer* 2006;107;451 – 8 (PV); Lengfelder E, et al. *Leuk Lymphoma* 1996;Suppl 1:135 – 42 (ET); Tefferi A, et al. *Blood* 2001;97:1896 (MF).

INTERFERON ALFA (PEGYLATED)

PEG-Interferon –α–2b	50 – 150 mg[1]	SQ	Weekly
	OR		
PEG-Interferon–α-2b	0.5 mcg/kg[2]	SQ	Weekly

Titrate dose to reach desired effect.

References: [1]Langer C, et al. *Haematologica* 2005;90:1333 – 8 (ET); [2]Samuelsson J, et al. *Cancer* 2006;106: 2397 – 405 (PV and ET); Quintas-Cardama A, et al. *Semin Thromb Hemos*. 2006;32:409 – 16 Review (various MPD).

IMATINIB
SEE MALIGNANT HEMATOLOGY SECTION

LENALIDOMIDE

Lenalidomide	10 mg	PO	Daily

NOTE: Use 5 mg daily if initial platelet count was less than 100 x 10^9/L.

Therapy continued for 3–4 months prior to assessment of efficacy. If benefit, continue therapy for additional 3 – 24 months or intolerance.

Reference: Tefferri A, et al. *Blood* 2006;108:1158 – 64 (MF).

MEPOLIZUMAB

Mepolizumab	750 mg	IV	Day 1

NOTE: Corticosteroids (prednisone) therapy was tapered throughout the period of treatment. Prednisone dose tapering began at 60 mg/d and was intended to be completely off by week 32 of therapy (i.e., last dose of mepolizumab). Specific instructions for tapering can be found in the manuscript.

Repeat cycle every 4 weeks for a total of 9 doses.

Reference: Rothenberg ME, et al. *N Engl J Med* 2008;358:1215 – 28 (HES).

THALIDOMIDE[1] or THALIDOMIDE – PREDNISONE[2]

Thalidomide	200 mg	PO*	Daily

OR

Thalidomide	50 mg	PO	Daily
Prednisone	0.5 mg/kg	PO**	Daily

*Titrate dose by 200 mg weekly to best tolerated response or 800 mg/day; **Taper slowly to off over 3 months.

References: [1]Thomas DA, et al. *Cancer* 2006;106:1974 – 84 (MF); [1]Abgrall JF, et al. *Haematologica* 2006;91:1027 – 32 (MF); [2]Mesa RA, et al. *Blood* 2003;101: 2534 – 41 (MF).

For references of other therapies used in the treatment of myelofibrosis (i.e., androgens, corticosteroids, and alkylating agents) refer to Arana–Yi C, et al. *Oncologist* 2006;11:929 – 43.

ANAGRELIDE
(AGRYLN®)

FDA approved for the treatment of essential thrombocytosis and thrombocytosis secondary to myeloproliferative disorders such as PV and CML. It appears to be unique in its ability to reduce platelet counts without affecting white or red blood cells or promoting the development of leukemia.

I. MECHANISM OF ACTION

Anagrelide exerts a thrombocytopenic effect as well as inhibits platelet aggregation. The thrombocytopenic effect appears to be a result of inhibition of megakaryocyte development in the late, post-mitotic stage. The thrombocytopenic effects appear to be specific for humans. At dosages higher than those required to produce thrombocytopenia in humans, anagrelide affects platelet aggregation by inhibiting cyclic nucleotide phosphodiesterase and the release of arachidonic acid from phospholipase, possibly by inhibiting phospholipase A2. This leads to increased platelet concentrations of cyclic adenosine monophosphate (cAMP). Anagrelide also inhibits collagen-induced platelet aggregation.

II. PHARMACOKINETICS

A) Peak plasma concentrations occur in about 1 hour and decrease rapidly during the first 6 – 8 hours.
B) Food reduces bioavailability.
C) Plasma elimination half-life is 1.3 hours under fasting conditions and is increased to 1.8 hours when administered with food. The terminal elimination half-life (T1/2-beta) is approximately 3 — 4 days.
D) A pharmacokinetic study of a single dose of anagrelide in subjects with moderate hepatic impairment showed an 8-fold increase in the area under the curve of anagrelide. The use of anagrelide in patients with severe hepatic impairment has not been studied, and use in this population is contraindicated.

III. DOSAGE AND ADMINISTRATION

A) Recommended starting dose is 0.5 mg orally QID or 1mg orally BID.
B) Dose is adjusted to maintain target platelet count.
C) Typical dose is 1.5 – 3 mg/day.
D) Do not increase dose more than 0.5 mg/week.
E) Maximum recommended dose is 10 mg/week.
F) In patients with moderate hepatic impairment, initial dosing is 0.5 mg PO once daily for a minimum of 1 week.
G) FDA pregnancy risk category C.

IV. TOXICITY

A) Headache (45%)
B) Palpitations (27%)
C) Diarrhea (24%)
D) Asthenia (22%)
E) Abdominal pain (18%)
F) Dizziness (15%)
NOTE: Serious adverse cardiac events ranging from arrhythmias, heart failure, and myocardial infarction have been reported. Anagrelide should be used with caution in patients with underlying cardiac history. Hematologic toxicity including anemia and thrombocytopenia has been reported in less than 5% of patients.

V. CLINICAL MONITORING
A) CBC
B) Electrolytes and liver function tests

VI. DRUG INTERACTIONS
Anagrelide is partially metabolized by CYP1A2. In theory, drugs that either inhibit or induce CYP1A2 could adversely affect the clearance of anagrelide. Anagrelide demonstrates some inhibitory activity of CYP1A2, and theoretically may affect the clearance of drugs metabolized by CYP1A2. Formal drug interaction studies between anagrelide and other drugs have not been conducted

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

ECULIZUMAB

Eculizumab	600 mg	IV*	Day 1, 8, 15, and 22

Followed by

Eculizumab	900 mg	IV*	Day 28

Followed by

Eculizumab	900 mg	IV*	Every 14 days onwards

*Administer over 35 minutes.

References: Hillmen P, et al. *N Eng J Med* 2004;350:552 – 9; Hillmen P, et al. *N Eng J Med* 2006;355:1233 – 43; Brodsky RA, et al. *Blood* 2008;111:1840 – 7.

ECULIZUMAB
(SOLIRIS™)

FDA was approved in March 2007 as an orphan drug for paroxysmal nocturnal hemoglobinuria (PNH), a rare, life-threatening, and genetically acquired form of hemolytic anemia. Patients must be vaccinated against *Neisseria meningitidis* prior to initiating treatment with eculizumab. In patients that have not been previously vaccinated, a meningococcal vaccine must be administered at least 2 weeks prior to the first dose of eculizumab and all patients should be revaccinated according to the current vaccination guidelines. Prior to initiating treatment with eculizumab, patients and prescribers must be enrolled in the Soliris™ Safety Registry, which is part of a special risk management program that involves initial and continuing education as well as long-term monitoring for the detection of new safety findings.

I. MECHANISM OF ACTION

Eculizumab is a monoclonal antibody designed to selectively block terminal complement activation and, thus, restore complement inhibition in the blood of patients with PNH. Specifically, eculizumab is a long-acting C5 terminal complement inhibitor. A genetic mutation in patients with PNH causes the formation of PNH cells or abnormal red blood cells, which are deficient in terminal complement inhibitors. The deficiency in terminal complement inhibitors causes the PNH cells to be sensitive to lysis by terminal complements leading to intravascular hemolysis. Eculizumab binds to the terminal complement protein C5 with high affinity, which inhibits its cleavage into C5a and C5b and prevents the generation of the terminal complement complex C5b-9. In patients with PNH, eculizumab inhibits intravascular hemolysis mediated by terminal complements

II. PHARMACOKINETICS

A.) Clearance rate of 22 mL/hr with a volume of distribution of 7.7 L.
B.) The mean half-life was 272 ± 82 hours
C.) The mean observed peak serum concentration by week 26 was 194 ± 76 mcg/mL; the mean observed trough concentration was 97 ± 60 mcg/ml. It appears that a trough serum concentration of $>= 35$ mcg/ml is required for terminal complement to be inhibited ($<= 20\%$ hemolytic activity) and to prevent hemolysis.
D.) Studies have not been conducted in children or elderly patients; the pharmacokinetics have not been evaluated in different races, genders, or disease states (e.g., hepatic or renal impairment).

III. DOSAGE AND ADMINISTRATION

A.) Recommended starting dose is 600 mg IV infusion every 7 days for the first 4 weeks, followed by a single dose of 900 mg IV infusion 7 days after the 4th dose, and then 900 mg IV infusion every 14 days.
B.) Administered via IV infusion over 35 minutes
C.) Monitor patients for allergic reactions during the infusion and for at least 1 hour after the infusion has ended. If an allergic reaction occurs, the infusion may be slowed or stopped. If the infusion is slowed, the total administration time should not exceed 2 hours.
D.) Pregnancy category C

IV. TOXICITY
A.) Headache (44%), nasopharyngitis (23%), back pain (19%), nausea/vomiting(16%), fatigue (12%), cough (12%), constipation (7%), myalgia (7%), extremity pain (7%), and influenza-like illness.
B.) Hypersensitivity reactions, including anaphylactoid reactions, are possible. During clinical trials, no patients experienced infusion related reactions requiring drug discontinuation.
C.) Herpes simplex infection (7% eculizumab vs. 0% placebo), sinusitis (7% vs. 0%), and respiratory tract infection (7% vs. 2%) were reported more commonly in patients receiving eculizumab vs. placebo during clinical trials.
D.) Serious *Neisseria meningitides* infections have been noted in both vaccinated and unvaccinated patients.
E.) Patients who discontinue treatment with eculizumab may be at increased risk of hemolysis

V. CLINICAL MONITORING
A.) CBC
B.) LDH
C.) Urine hemoglobin
D.) Other markers of hemolysis

VI. DRUG INTERACTIONS
A.) Drug interaction studies have not been conducted with eculizumab.
B.) During clinical trials, patients have received concomitant cyclosporine, warfarin, heparin, corticosteroids, and erythropoietin