Understanding Polycythemia Vera and Myelofibrosis:
A Practical Guide for Advanced Practice Providers
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MYELOPROLIFERATIVE NEOPLASMS
Myeloproliferative neoplasms are a distinct group of hematologic malignancies

Myeloproliferative neoplasms (MPNs) are a group of rare blood cancers classified by the presence or absence of the Philadelphia chromosome (Ph) (which contains the BCR-ABL fusion gene characteristic of chronic myeloid leukemia).1,2

Ph-negative MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). These 3 neoplasms share molecular and cellular characteristics but differ in phenotype and clinical presentation.2

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**Myeloid Neoplasms and Acute Leukemias3,4a**

- **Myelodysplastic syndromes**
- **Myeloproliferative neoplasms**
- **Acute myeloid and related leukemias**
- **Lymphoblastic leukemias/lymphomas**

**Philadelphia chromosome (+)**
- Chronic myeloid leukemia (CML)
  - ~58,000 people in the US5
- Polycythemia vera (PV)
  - ~100,000 people in the US5
  - ~10% transformation rate per 10 years7

**Philadelphia chromosome (-)**
- Essential thrombocythemia (ET)
  - ~71,000-88,000 people in the US6
  - ~4% transformation rate per 10 years7
- Post-PV MF
- Primary Myelofibrosis (MF)
- Post-ET MF

~16,000 to 18,500 people in the United States6

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WHO, World Health Organization.

* Select disease entities from the 2016 WHO classification of myeloid neoplasms and acute leukemias, which include myeloproliferative neoplasms, mastocytosis, myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFA, PDGFB, or FGFR1, or with PCM1-JAK2, myelodysplastic/myeloproliferative neoplasms, myelodysplastic syndromes, myeloid neoplasms with germ line predisposition, acute myeloid leukemia and related neoplasms, acute leukemias of ambiguous lineage, B-lymphoblastic leukemia/lymphoma, and T-lymphoblastic leukemia/lymphoma.7
Myeloproliferative neoplasms are characterized by overproliferation of myeloid blood cells

Hematologic malignancies can arise from either myeloid or lymphoid cell lineages. MPNs in particular are characterized by increased clonal proliferation of myeloid cells in the bone marrow. Unregulated proliferation may occur in one or more myeloid cell lines, including erythrocytes, platelets, and/or granulocytes. 

Myeloid malignancies arise from clonal transformations within this pathway and result in changes in proliferation and differentiation of RBCs, platelets, and WBCs. Examples include:
- Myeloproliferative neoplasms
- Myelodysplastic syndromes
- Acute myeloid leukemia
- Chronic myeloid leukemia

Lymphoid malignancies arise from clonal transformations within this pathway and result in changes in differentiation of lymphocytes. Examples include:
- Acute lymphocytic leukemia
- Chronic lymphocytic leukemia
- Hairy cell leukemia
- Non-Hodgkin lymphoma
- Hodgkin lymphoma

MPN, myeloproliferative neoplasm; RBC, red blood cell; WBC, white blood cell.
I. JAK/STAT is a key signaling pathway in hematopoietic cells

Under normal conditions, hematopoietic cells are activated to mature and multiply when cytokines bind to cell-surface receptors, initiating a signaling cascade through the JAK/STAT pathway.²

Inside the cell, receptor-bound JAKs (Janus-associated kinases) activate proteins called STATs (signal transducer and activator of transcription), which form dimers and enter the nucleus. STATs bind to DNA, stimulating gene expression related to cell survival, differentiation, and proliferation.²

• **JAK1**: Plays an important role in signaling of key proinflammatory cytokines¹⁰
• **JAK2**: Mediates signals for hematopoietic growth factors¹⁰

JAK, Janus-associated kinase; STAT, signal transducer and activator of transcription.
JAK/STAT pathway mutations lead to overactive signaling

In PV and MF, mutations such as JAK2, CALR, and MPL lead to JAK/STAT pathway activation even when pathway-stimulating cytokines are not present.\textsuperscript{11-13} Upregulation of cytokines following prolonged signaling perpetuates this pathway even in receptors with unmutated JAKs.\textsuperscript{13}

<table>
<thead>
<tr>
<th>Driver Mutation</th>
<th>Prevalence in PV</th>
<th>Prevalence in MF</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2</td>
<td>~95%</td>
<td>50%-60%</td>
</tr>
<tr>
<td>CALR</td>
<td>&lt;1%</td>
<td>25%-30%</td>
</tr>
<tr>
<td>MPL</td>
<td>&lt;1%</td>
<td>3%-5%</td>
</tr>
</tbody>
</table>

Feedback loop: Upregulation of cytokines following prolonged signaling perpetuates this pathway.
II.

POLYCYTHEMIA VERA
Overactive JAK/STAT pathway signaling is a key mechanism of disease in PV

In PV, the JAK/STAT pathway becomes overactive typically as a result of JAK2 mutations; the excess cytokines produced perpetuate the pathway even in cells with unmutated JAKs.\textsuperscript{10,11,13}

Dysregulated signaling may result in\textsuperscript{3,14}:
- Elevated Hct (erythrocytosis)
- Elevated WBCs (leukocytosis)
- Elevated platelets (thrombocytosis)
- Inflammation
- Procoagulation state contributing to thrombotic risk
- PV-associated symptom burden and splenomegaly

\textbf{Overview of Polycythemia Vera}

\textit{Hct}, hematocrit; JAK, Janus-associated kinase; PV, polycythemia vera; STAT, signal transducer and activator of transcription; WBC, white blood cell.
II. Thrombosis is associated with morbidity and mortality in patients with PV

Known Causes of Death (n = 164)\textsuperscript{15a}

- Thrombotic complication: 20%
- Acute leukemia: 22%
- Second malignancy: 22%
- Heart failure: 8%
- Non-leukemic progression: 7%
- Other\textsuperscript{b}: 21%

Associated Morbidities\textsuperscript{16}

<table>
<thead>
<tr>
<th>Arterial Thrombosis</th>
<th>Venous Thrombosis</th>
<th>Microcirculatory Disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myocardial infarction</td>
<td>• Deep venous thrombosis (legs and arms)</td>
<td>• Erythromelalgia</td>
</tr>
<tr>
<td>• Unstable angina</td>
<td>• Pulmonary embolism</td>
<td>• Seizures</td>
</tr>
<tr>
<td>• Ischemic stroke</td>
<td>• Unusual sites of venous thrombosis (visceral vein</td>
<td>• Migraine</td>
</tr>
<tr>
<td>• Transient ischemic attack</td>
<td>thrombosis and cerebral sinus and venous thrombosis)</td>
<td>• Vertigo</td>
</tr>
<tr>
<td>• Acute peripheral and visceral thromboembolism</td>
<td>• Superficial venous thrombosis</td>
<td>• Tinnitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Scintillating scotomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Amaurosis fugax</td>
</tr>
</tbody>
</table>

Thrombotic events represent one of the most common causes of death in PV.\textsuperscript{15,17-19}

PV, polycythemia vera.

\textsuperscript{a} Cause of death was examined in a large, retrospective, international study of 1545 patients with PV; 347 (23%) had died by the time of analysis, of which 164 had a known cause of death.

\textsuperscript{b} Other causes included infection (n = 7), respiratory failure (n = 7), bleeding (n = 5), end-stage liver disease (n = 3), cardiopulmonary arrest (n = 3) and other causes with incidences of 2 or less (n = 10).
Evidence from the CYTO-PV study

**Elevated Hct between 45% and 50%: 4-fold higher rate of cardiovascular death and major thrombosis**

Managing Hct levels between 45% and 50% significantly increased the risk of cardiovascular death and major thrombosis compared with Hct levels managed to <45% (HR, 3.91; 95% CI, 1.45 to 10.53; \( P = 0.007 \)).

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>Low Hct (&lt;45%)</th>
<th>High Hct (45%-50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Hct</td>
<td>5/182 (2.7%)</td>
<td>18/183 (9.8%)</td>
</tr>
<tr>
<td>High Hct</td>
<td>1.00</td>
<td>3.91 (95% CI, 1.45-10.53)</td>
</tr>
</tbody>
</table>

Probability of Remaining Event-Free in the CYTO-PV Study (N = 365)


CI, confidence interval; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; Hct, hematocrit; HR, hazard ratio; PV, polycythemia vera.

* In the CYTO-PV study of 365 adult patients with PV treated with phlebotomy, hydroxyurea, or both, patients were randomized to 1 of 2 groups—either the low-Hct group (n = 182; with more intensive therapy to maintain a target Hct level <45%) or the high-Hct group (n = 183; with less intensive therapy to maintain a target Hct level of 45% to 50%). Baseline characteristics were balanced between the groups. Approximately 50% of patients had received an initial diagnosis of PV within 2 years prior to randomization. 67.1% of patients (n = 245) were at high risk because of age >65 years or previous thrombosis. The composite primary endpoint was the time until cardiovascular death or major thrombosis.
Additional analysis from the CYTO-PV study

**Elevated WBC counts >11 × 10^9/L increased the risk of thrombosis**

In a multivariable time-dependent analysis, WBC count >11 × 10^9/L was associated with increased risk of thrombosis (HR, 3.9; 95% CI, 1.24-12.3; \( P = 0.02 \))

- In this analysis, there was a trend for increased risk of thrombosis with WBC count >7 × 10^9/L (ie, HR >1) that became statistically significant in patients with WBC counts >11 × 10^9/L.
- These results are consistent with other literature that suggests leukocytosis may increase the risk of thrombosis.

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**Blood Counts and Thrombotic Risk**

- **CI, confidence interval; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; Hct, hematocrit; HR, hazard ratio; PV, polycythemia vera; WBC, white blood cell.**
- **a Adjusted for age, gender, cardiovascular risk factors, previous thrombosis, and Hct levels.**
In the prospective, observational REVEAL study,

The estimated 4-year mortality rate was 14% in patients with high-risk PV\(^{24a}\)

- 86% of high-risk patients (1660/1940) received HU and/or PBT at enrollment\(^{25}\)

### Overall survival by risk category at enrollment in the REVEAL study\(^{24b}\)

<table>
<thead>
<tr>
<th>Years</th>
<th>Patients at risk, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1936</td>
</tr>
<tr>
<td>0.5</td>
<td>1882</td>
</tr>
<tr>
<td>1.0</td>
<td>1806</td>
</tr>
<tr>
<td>1.5</td>
<td>1694</td>
</tr>
<tr>
<td>2.0</td>
<td>1623</td>
</tr>
<tr>
<td>2.5</td>
<td>1538</td>
</tr>
<tr>
<td>3.0</td>
<td>1453</td>
</tr>
<tr>
<td>3.5</td>
<td>1106</td>
</tr>
<tr>
<td>4.0</td>
<td>604</td>
</tr>
<tr>
<td>4.5</td>
<td>137</td>
</tr>
<tr>
<td>5.0</td>
<td>0</td>
</tr>
</tbody>
</table>

(58/175) of patients died due to vascular-related complications, which were the most common cause of death\(^{24}\)

Estimated 4-year mortality rate\(^{24c}\):
- 3% low-risk
- 14% high-risk

In the 6 months before death\(^{24}\)

- (110/190) of patients had ≥1 elevated WBC count >11 × 10\(^9\)/L\(^c\)
- (59/190) of patients had ≥1 elevated Hct level >45%

Hct, hematocrit; HU, hydroxyurea; PBT, phlebotomy; PV, polycythemia vera; WBC, white blood cell.

\(^{a}\) 77% of patients (1940/2510) were classified as high risk at enrollment based on age ≥60 years and/or history of thrombotic events.\(^{25}\)

\(^{b}\) REVEAL was a prospective, observational study of 2510 adult patients with PV in the United States, sponsored by Incyte. Patients were enrolled over an approximate 2-year period (July 2014 to August 2016). This analysis included all enrolled patients and evaluated characteristics of deceased patients, survival by risk, and causes of death over the course of the study. A total of 244 patients died during the study, with 190 having available Hct values and WBC counts in the 6 months before death, and 175 having a known cause of death. Among the 244 patients who died during the study, 82% (n = 200) were categorized as high risk at diagnosis, primarily due to age ≥60 years only (65%; n = 159).\(^{24}\)

\(^{c}\) 71% (78/110) of these patients did not experience an infection in the year prior to death.\(^{6}\)
In the prospective, observational REVEAL study, some patients continued to have elevated counts despite treatment with hydroxyurea (HU) alone.

Elevated Laboratory Values in Patients Who Received HU for ≥3 Months in the REVEAL Study

- The median of the maximum Hct value among evaluable patients (n = 1106) who received HU for ≥3 months was:\(^\text{27}\):
  - 48.3% for those who reported a value >45%
  - 42% for those who reported a value ≤45%

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Hct, hematocrit; HU, hydroxyurea; PLT, platelet; PV, polycythemia vera; WBC, white blood cell.

\(^{26\text{a}}\) REVEAL was a prospective, observational study of 2510 patients with PV in the US, sponsored by Incyte. This analysis focused on blood count control in the subset of 1381 patients who had received HU for ≥3 months.
In the prospective, observational REVEAL study, Patients who were treated with HU and receiving phlebotomy (PBT) were more likely to have elevated blood counts

**Elevated Laboratory Values by PBT Within 3 Months of Enrollment and HU Exposure**

- After at least 3 months of HU, 33.1% (457/1381) of patients continued to receive PBTs
  - 83% of these patients requiring PBTs continued to report Hct values >45%
- Additionally, another study showed PBT requirement while on HU therapy is an independent risk factor for thrombosis
  - In an observational study of 533 patients with PV, a significantly higher rate of thrombosis was found in patients treated with HU plus 3 or more PBTs per year compared to HU plus 0-2 PBTs per year (20.5% vs 5.3% at 3 years; \( P < 0.0001 \))

Hct, hematocrit; HU, hydroxyurea; PBT, phlebotomy; PLT, platelet; PV, polycythemia vera; WBC, white blood cell.

*R E V E A L  was a prospective, observational study of 2510 patients with PV in the US, sponsored by Incyte. This analysis focused on blood count control in the subset of 1381 patients who had received HU for ≥3 months.*
Clinical case: Eve, a 75-year-old female

Past history
- Diagnosed at age 67 years
- Referred due to elevated Hb and Hct on routine CBC
- Complained of mild itching, moderate headaches, moderate night sweats
- No history of thrombotic event
- At diagnosis, management consisted of low-dose aspirin and PBT once every 4 weeks
- 1 year and 5 months after diagnosis, HU was initiated at 500 mg/day

Recent visits

<table>
<thead>
<tr>
<th>6 years, 3 months (Post-HU Initiation)</th>
<th>7 years (Post-HU Initiation)</th>
<th>7 years, 3 months (Post-HU Initiation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labs</td>
<td>Symptoms</td>
<td>Treatment</td>
</tr>
<tr>
<td>Hct: 46.6%</td>
<td>Mild fatigue</td>
<td>HU 1000 mg/day (MTD)</td>
</tr>
<tr>
<td>WBC: 21.4 x 10^9/L</td>
<td>Moderate headaches</td>
<td>PBT</td>
</tr>
<tr>
<td>PLT: 391 x 10^9/L</td>
<td></td>
<td>Low-dose aspirin</td>
</tr>
<tr>
<td>Hct: 49.6%</td>
<td>Mild fatigue</td>
<td>HU 1000 mg/day (MTD)</td>
</tr>
<tr>
<td>WBC: 15.7 x 10^9/L</td>
<td>Moderate headaches</td>
<td>PBT</td>
</tr>
<tr>
<td>PLT: 501 x 10^9/L</td>
<td></td>
<td>Low-dose aspirin</td>
</tr>
</tbody>
</table>

Eve’s Hct and WBC counts were elevated while receiving treatment with HU and phlebotomy. In addition to her age, her elevated Hct and WBC counts may have increased her risk for a thrombotic event, contributing to her myocardial infarction.
A majority of patients with PV reported that symptoms impact quality of life²⁹-³¹

PV-related symptoms are prevalent and may impact a patient’s quality of life²⁹-³¹

- **Fatigue**: 88%
- **Inactivity**: 61%
- **Night sweats**: 52%
- **Bone pain**: 50%
- **Itching**: 62%
- **Abdominal discomfort**: 51%
- **Early satiety**: 64%
- **Fever**: 18%
- **Concentration problems**: 65%
- **Weight loss**: 31%

Type of symptom
- Cytokine-related
- Hyperviscosity-related
- Splenomegaly-related

In the MPN Landmark Survey,³¹ᵇ
66% of patients with PV reported that their symptoms diminished their quality of life³¹ᶜ

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² This prospective study included a total of 1433 patients with MPNs (n = 538 with PV), who were queried on the 10 symptoms from the MPN-SAF TSS/MPN-10. The MPN-SAF TSS is validated for serial tracking of the most pertinent MPN-related symptoms—fatigue, concentration problems, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever—scored on a scale of 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be), for a total possible score of 100.³⁰

³ The MPN Landmark Survey, funded by Incyte Corporation, was a web-based questionnaire composed of 65 multiple-choice questions intended to help evaluate the patient disease burden in the MPN disease setting. A total of 813 patients in the United States with a previous diagnosis of PV (n = 380), MF (n = 207), or ET (n = 226) completed the survey.³¹

³¹ This prospective study included a total of 1433 patients with MPNs (n = 538 with PV), who were queried on the 10 symptoms from the MPN-SAF TSS/MPN-10. The MPN-SAF TSS is validated for serial tracking of the most pertinent MPN-related symptoms—fatigue, concentration problems, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever—scored on a scale of 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be), for a total possible score of 100.³⁰

³¹ᵇ The MPN Landmark Survey, funded by Incyte Corporation, was a web-based questionnaire composed of 65 multiple-choice questions intended to help evaluate the patient disease burden in the MPN disease setting. A total of 813 patients in the United States with a previous diagnosis of PV (n = 380), MF (n = 207), or ET (n = 226) completed the survey.³¹

³¹ᶜ Patients reported whether they strongly agreed, somewhat agreed, somewhat disagreed, or strongly disagreed with the following statement: PV symptoms reduce my quality of life.³¹
On average, patients with known HU use had a moderately high symptom burden (TSS = 29.2)\textsuperscript{32}

A prospective study of 1334 patients with PV where a subset of patients received HU (n = 499)\textsuperscript{32a}

**MPN-10 Mean Symptom Scores in Patients With Known HU Use\textsuperscript{32}**

![Graph showing MPN-10 Mean Symptom Scores in Patients With Known HU Use](image-url)

HU, hydroxyurea; MPN, myeloproliferative neoplasm; MPN-SAF TSS/MPN-10, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PBT, phlebotomy; PV, polycythemia vera.

\textsuperscript{32} A prospective study of 1334 patients with PV was conducted to assess baseline symptoms with certain disease features (ie, known HU use, known PBT requirements, and splenomegaly), and compared to a control group of patients who lacked the specified feature. The patients had the following characteristics: known HU use (n = 499), known PBT (n = 646), palpable splenomegaly (n = 369), or all 3 features (n = 148). Assessment of MPN symptoms was performed by using the MPN-SAF TSS/MPN-10. All items were evaluated on a 0 (absent) to 10 (worst imaginable) scale. The MPN-10 TSS has a possible range of 0 to 100 with 100 representing the highest level of symptom severity. The TSS for each patient was analyzed to place the patient into the quartiles of low symptom burden (TSS, 0 to 7), intermediate symptom burden (TSS, 8 to 17), moderately high symptom burden (TSS, 18 to 31), or high symptom burden (TSS, ≥32).\textsuperscript{32}
Patients with PV had moderately high symptom burden regardless of blood count control

Symptom burden in patients who achieved blood count control vs those who did not was analyzed among 1813 evaluable patients with PV in the prospective, observational REVEAL study.33

Mean Total Symptom Score According to Blood Count Control Status (Hct, WBC, PLT)33

<table>
<thead>
<tr>
<th>Blood Count Control Status</th>
<th>TSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 3 controlled (CHR)</td>
<td>19.1</td>
</tr>
<tr>
<td>≥2 controlled</td>
<td>18.7</td>
</tr>
<tr>
<td>≥1 controlled</td>
<td>18.7</td>
</tr>
<tr>
<td>All 3 uncontrolled</td>
<td>20.2</td>
</tr>
</tbody>
</table>

Total Symptom Score key32,34

0-7: Low symptom burden
8-17: Intermediate symptom burden
18-31: Moderately high symptom burden
≥32: High symptom burden

CBC, complete blood count; CHR, complete hematologic response; Hct, hematocrit; HU, hydroxyurea; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PBT, phlebotomy; PLT, platelet; PV, polycythemia vera; WBC, white blood cell.

REVEAL was a prospective, observational study that collected contemporary data regarding burden of disease, clinical management, patient-reported outcomes, and healthcare resource utilization from 2510 adult patients with PV in the United States and was sponsored by Incyte. Patients were enrolled over an approximate 2-year period (July 2014 to August 2016). This analysis included 1813 (72.2%) evaluable patients who had a CBC within 30 days before completion of the at-enrollment MPN-SAF TSS. At the time of enrollment, most patients (n = 1714; 94.5%) were being managed with cytoreductive therapy; 1581 patients (87.2%) were managed with PBT, HU, or a combination thereof. CHR was defined as Hct <45%, WBC count <10 × 10⁹/L, and PLT count ≤400 × 10⁹/L; these same criteria were used to determine if Hct, WBC, and PLT were controlled.33

Republished from Clinical Lymphoma Myeloma & Leukemia, 19(9), Grunwald MR, Burke JM, Kuter DJ, et al, Symptom burden and blood counts in patients with polycythemia vera in the United States: an analysis from the REVEAL Study, 579-584, Copyright 2019, with permission from Elsevier.
Clinical case: Ron, an 88-year-old male

Past history

- Diagnosed with PV at age 86 years after hospital admission for DVT
- Considered high risk because of age and prior thrombotic event
- Symptoms: severe itching, moderate night sweats and fatigue, mild concentration problems, headaches, and dizziness
- At diagnosis, management consisted of HU 1000 mg/day, low-dose aspirin, and PBT weekly
- Planned follow up was every 2 months

Recent visits

<table>
<thead>
<tr>
<th>9 months (Post-HU Initiation)</th>
<th>14 months (Post-HU Initiation)</th>
<th>19 months (Post-HU Initiation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labs</td>
<td>Symptoms</td>
<td>Treatment</td>
</tr>
<tr>
<td>Hct: 46.5%</td>
<td>Moderate itching and fatigue</td>
<td>HU 1000 mg/day</td>
</tr>
<tr>
<td>WBC: 11.6 × 10^9/L</td>
<td>Mild night sweats and dizziness</td>
<td>Phlebotomy as needed</td>
</tr>
<tr>
<td>PLT: 235 × 10^9/L</td>
<td></td>
<td>Low-dose aspirin</td>
</tr>
<tr>
<td>Symptoms</td>
<td>MILD to moderate itching</td>
<td>HU 2000 mg/day (MTD)</td>
</tr>
<tr>
<td></td>
<td>Mild fatigue, night sweats and</td>
<td>Phlebotomy as needed</td>
</tr>
<tr>
<td></td>
<td>dizziness</td>
<td>Low-dose aspirin</td>
</tr>
<tr>
<td>Labs</td>
<td>MILD itching</td>
<td>HU 2000 mg/day (MTD)</td>
</tr>
<tr>
<td>Hct: 45.0%</td>
<td>Majestic ting</td>
<td>Phlebotomy as needed</td>
</tr>
<tr>
<td>WBC: 7.8 × 10^9/L</td>
<td>Fatigue</td>
<td>Low-dose aspirin</td>
</tr>
<tr>
<td>PLT: 160 × 10^9/L</td>
<td>Night sweats</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>MILD to moderate itching</td>
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<tr>
<td></td>
<td>Fatigue, night sweats and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dizziness</td>
<td></td>
</tr>
<tr>
<td>Labs</td>
<td>MILD itching</td>
<td></td>
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<tr>
<td>Hct: 45.5%</td>
<td>Fatigue</td>
<td></td>
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<tr>
<td>WBC: 12.3 × 10^9/L</td>
<td>Night sweats</td>
<td></td>
</tr>
<tr>
<td>PLT: 170 × 10^9/L</td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>MILD itching</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Night sweats</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
</tr>
</tbody>
</table>

Ron’s itching and fatigue had worsened while on HU 2000 mg/day, which may suggest disease progression. He also continued to experience night sweats on HU therapy. Due to Ron’s elevated counts and persistent symptoms, a change in management approach was discussed.

DVT, deep vein thrombosis; Hct, hematocrit; HU, hydroxyurea; MTD, maximum tolerated dose; PBT, phlebotomy; PLT, platelet; PV, polycythemia vera; WBC, white blood cell.

This case is based on an actual patient. All patient data have been deidentified.
## Enhance your conversations about PV-related symptoms with contextual questions

Patients with PV may not recognize that their symptoms may be related to their cancer.\(^{25}\)

Open-ended questions can encourage your patients to express their symptom burden and severity based on what they experience in daily life.

### Fatigue and Inactivity

- Are there activities that you were able to do 3 months ago that you struggle with now?
- How much does your fatigue or inactivity influence your day-to-day activities? Your enjoyment of life?

### Day or Night Sweats

- Do you experience sweating, particularly at night or in the evenings?
- Does this require you to change your sheets or clothing?
- Does this wake you up or impact your sleep?
- How often did this happen in the past month?

### Itching

- Have you noticed changes in your skin, particularly itching?
- When you shower, do you ever feel itchy afterwards? How often?
- Have you found yourself taking shorter/fewer/cooler showers to try to avoid itchiness?

### Concentration Problems

- How often have you felt a “brain fog”—memory lapses (such as problems remembering words or dates) or generally having problems concentrating?
- How has this impacted your life? Have you had to change school plans, work, or how you function at home?

Caregivers can be a valuable source of information. They often see the impact of PV-related symptoms on a patient’s quality of life or daily activity.

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### A complete list of contextual questions for assessing symptoms in patients with PV can be found in the Resources Section.

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PV, polycythemia vera.
II.

Actively monitor your patients for clinical characteristics of advanced PV

PV is a hematologic malignancy that may become advanced in a subset of patients despite treatment with HU and PBT, resulting in ineffective disease control\textsuperscript{36-39}

<table>
<thead>
<tr>
<th>Hct +</th>
<th>Elevated Hct levels $\geq 45%$ plus one additional factor—despite treatment with HU$^{40a}$ and phlebotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elevated WBC counts$^{21}$ $&gt;11 \times 10^9$/L</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Burdensome disease-related symptoms$^{30}$ (such as fatigue, early satiety, inactivity, concentration problems, and itching)</td>
</tr>
</tbody>
</table>

- In PV, overactive JAK/STAT pathway signaling leads to blood cell overproliferation and inflammation that increases thrombotic risk, as well PV-related symptoms resulting from proinflammatory cytokines, blood hyperviscosity, and splenomegaly
- Thrombotic events represent one of the most common causes of death in PV
- In the CYTO-PV study, elevated Hct between 45% and 50% was associated with a 4-fold higher rate of cardiovascular death and major thrombosis compared with Hct <45%
- In an additional analysis from the same study, elevated WBC counts $>11 \times 10^9$/L were associated with an increased risk of thrombosis
- Symptom burden in patients with PV can be substantial and may not be adequately controlled with HU
- Contextual questions can help detect changes in a patient’s symptom burden and impact on quality of life

\textsuperscript{a} After maximum tolerated dose of HU.

Hct, hematocrit; HU, hydroxyurea; JAK, Janus-associated kinase; PBT, phlebotomy; PV, polycythemia vera; STAT, signal transducer and activator of transcription; WBC, white blood cell.
III. MYELOFIBROSIS
Overactive JAK/STAT pathway signaling is a key mechanism of disease in MF

Factors that impact JAK/STAT signaling include JAK2 mutations, MPL mutations, CALR mutations, excess cytokines, increased JAK1 signaling, and impaired negative signaling mechanisms.11,12,41

The signaling dysregulation leads to hematopoietic stem cell loss and bone marrow fibrosis. As the bone marrow becomes fibrotic, normal hematopoiesis can no longer occur, resulting in extramedullary hematopoiesis, particularly in the spleen.42,43
Splenomegaly is an important clinical indicator in MF\(^3\)

\(~90\%\) of patients with MF had palpable splenomegaly at diagnosis

Based on a study of 1054 patients with primary MF; data were available for 768 patients, 681 of whom had palpable splenomegaly\(^45\)

New or increasing splenomegaly is considered to be a marker of disease progression in MF.\(^{46}\)

**A palpable spleen of \(\geq 5\) cm below the LCM constitutes progressive disease\(^{46a}\)**

A growing spleen can cause or exacerbate MF-related symptoms.\(^{44,47}\)

- Splenomegaly may be associated with pain, early satiety, abdominal discomfort, and other symptoms\(^{43,44}\)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\(^®\)) for Myeloproliferative Neoplasms recommend palpating the spleen at diagnosis in all patients\(^48\)

- Imaging, including ultrasound, may be appropriate for patients with a body habitus that precludes palpation\(^49\)

CT, computed tomography; LCM, left costal margin; MF, myelofibrosis; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network.

\(^a\) According to the International Working Group-Myeloproliferative Neoplasms Research and Treatment and European LeukemiaNet response criteria. Progressive disease assignment for splenomegaly requires confirmation by CT or MRI showing a \(\geq 25\%\) increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to post-treatment measurements.\(^a\)
Majority of patients with MF report symptom burden at diagnosis\(^{31,50}\)

95\% of patients reported 2+ MF-related symptoms at diagnosis based on a retrospective chart review of 180 patients with MF\(^{50a}\)

- In the MPN Landmark survey, many patients with MF (49\%) reported experiencing symptoms at least 1 year before diagnosis\(^{31b}\)
- Symptoms may be present even in patients with earlier disease\(^{31,50}\)
- Constitutional symptoms are well-established negative predictors of survival in MF\(^{45,51c}\)

NCCN Guidelines\(^{®}\) for Myeloproliferative Neoplasms (MPNs) recommend assessing symptoms (in a provider’s office) at baseline and monitoring symptom status (stable, improved, or worsening). Changes in symptom status could be a sign of disease progression. Therefore, change in symptom status should prompt evaluation.

ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloprolif erative neoplasm; NCCN, National Comprehensive Cancer Network; PV, polycythemia vera.

\(^{a}\) Retrospective observational study of symptom burden and splenomegaly in 180 patients with MF; data were collected at the time of diagnosis of MF in patients without splenomegaly (n = 78) or at the time of detection of splenomegaly in patients with splenomegaly (n = 102). In patients with splenomegaly, splenomegaly was most often recorded at the time of diagnosis (median time from MF diagnosis to reported splenomegaly was 1 day).\(^{30}\)

\(^{b}\) The MPN Landmark Survey, funded by Incyte Corporation, was a web-based questionnaire composed of 65 multiple-choice questions intended to help evaluate the patient’s perception of disease burden in the MPN disease setting. A total of 813 patients in the United States with a previous diagnosis of PV (n = 380), MF (n = 207), or ET (n = 226) participated.\(^{31}\)

\(^{c}\) Constitutional symptoms are defined as >10\% weight loss in 6 months, night sweats, and/or unexplained fever higher than 37.5°C.\(^{47,51}\)
### MF-related symptoms are prevalent and may impact quality of life

The majority of patients with MF reported that symptoms impacted quality of life.

**Self-Reported Symptoms of MF**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>96%</td>
</tr>
<tr>
<td>Early satiety</td>
<td>77%</td>
</tr>
<tr>
<td>Inactivity</td>
<td>74%</td>
</tr>
<tr>
<td>Concentration problems</td>
<td>69%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>66%</td>
</tr>
<tr>
<td>Night sweats*</td>
<td>66%</td>
</tr>
<tr>
<td>Bone pain</td>
<td>52%</td>
</tr>
<tr>
<td>Itching</td>
<td>50%</td>
</tr>
<tr>
<td>Weight loss*</td>
<td>42%</td>
</tr>
<tr>
<td>Fever*</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Constitutional symptoms.

**Patient-reported results from the MPN Landmark Survey**:

- 81% of patients with MF reported that their symptoms reduced their quality of life.
- 79% reported that MF interfered with family or social life.

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ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; MPN-SAF TSS/MPN-10, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PV, polycythemia vera.

* This prospective study included a total of 1433 patients with MPNs (n = 293 with MF), who were queried on the 10 symptoms from the MPN-SAF TSS/MPN-10. The MPN-SAF TSS is validated for serial tracking of the most pertinent MPN-related symptoms—fatigue, concentration problems, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever—scored on a scale of 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be), for a total possible score of 100.

* The MPN Landmark Survey, funded by Incyte Corporation, was a web-based questionnaire composed of 65 multiple-choice questions intended to help evaluate the patient’s perception of disease burden in the MPN disease setting. A total of 813 patients in the United States with a previous diagnosis of PV (n = 380), MF (n = 207), or ET (n = 226) participated.

* Patients reported whether they strongly agreed, somewhat agreed, somewhat disagreed, or strongly disagreed with the following statement: MF symptoms reduce my quality of life.

* Patients reported impact on their activities of daily living on a scale that ranged from 1 (not at all) to 5 (a great deal). The patient was included as having interference with daily activities if they had ever experienced the issue and reported a score >1.
Enhance your conversations about MF-related symptoms with contextual questions

Patients with MF may not recognize that their symptoms may be related to their cancer. Open-ended questions, such as those shown below, can encourage your patients to express their symptom burden based on what they experience in daily life.

- Do you feel full quickly after meals?
- Have you lost weight in the past 6 months, without intentionally trying to?

**Early Satiety**

- Do you have abdominal discomfort, particularly after eating?
- Do you experience any dull or sharp pains in your abdomen?
- Do you experience abdominal discomfort at any other time?
- Do you find it difficult to get into a comfortable position for sleeping?

**Abdominal Discomfort**

- Do you feel tired even after getting enough sleep, or do you tire quickly during the day?
- How many normal waking hours each day do you spend in a bed or chair?
- Are there activities that you were able to do 3 months ago that you struggle with now?

**Fatigue and Inactivity**

- How often have you felt a “brain fog”—memory lapses, inability to pay attention for long periods, or generally having problems concentrating that interfere with your ability to work?
- How has this impacted your life? Have you had to change school plans, work, or how you function at home?

**Concentration Problems**

Caregivers can be a valuable source of information. They often see the impact of MF-related symptoms on a patient’s quality of life or daily activity.

A complete list of contextual questions for assessing symptoms in patients with MF can be found in the Resources Section.

MF, myelofibrosis.
Clinical case: Martha, a 57-year-old female

Martha’s complaints of fatigue and abdominal discomfort led to a workup that ultimately resulted in a diagnosis of primary MF. At diagnosis, her spleen was already palpable 5 cm below the LCM.

<table>
<thead>
<tr>
<th>Reason for referral</th>
<th>• Workup for complaints of fatigue and abdominal pain revealed splenomegaly on CT scan</th>
</tr>
</thead>
</table>
| Bloodwork           | • Hb: 10.2 g/dL  
• WBC: 7.2 \(\times\) 10^9/L  
• PLT: 284 \(\times\) 10^9/L  
• Peripheral blood smear: mild normochromic normocytic anemia, with rare blast noted |
| Bone marrow biopsy  | • Bone marrow biopsy: findings comparable with a diagnosis of primary MF  
• Mutation analysis: \(BCR-ABL\) negative, \(JAK2\) negative, \(MPL\) negative, \(CALR\) positive  
• Karyotype: no unfavorable karyotype |
| Spleen              | • Palpated 5 cm below the LCM |
| Symptoms            | • Fatigue, abdominal discomfort |

Martha presented with symptoms of fatigue and abdominal discomfort. On examination, an enlarged spleen measuring 5 cm below the LCM was found, which may indicate that her MF already progressed before diagnosis.
Actively monitor your patients with MF for splenomegaly and MF-related symptoms

- MF is a serious hematologic malignancy that arises from dysregulated JAK/STAT signaling and is characterized by substantial symptom burden and splenomegaly
- Splenomegaly is an important clinical indicator and should be assessed at diagnosis
- Symptoms should be monitored at baseline and during the course of disease, as changes in symptom status could be a sign of disease progression
IV. RESOURCES
Checklist for monitoring patients with PV

- Assess patients for thrombotic risk factors
- Actively monitor patients on HU for signs of inadequate response
- Maintain Hct <45%
- Watch for increasing WBC counts, especially $>11 \times 10^9$/L
- Actively monitor symptoms early in the disease course and over time, even if blood counts are not elevated
- Obtain a detailed picture of the patient’s symptom burden by asking open-ended questions about specific symptoms known to be associated with PV
- Empower patients and caregivers to take an active role in symptom identification by educating them about PV-related symptoms

Empower your patients with PV to take an active role in their care. Discuss the importance of:

- Proactively identifying signs of changes in their disease
- Keeping lab appointments to monitor blood counts
Contextual questions to ask your patients with PV

**CYTOKINE-RELATED SYMPTOMS**

**Fatigue and Inactivity**
- Are there activities that you were able to do 3 months ago that you struggle with now?
- How much does your fatigue or inactivity influence your day-to-day activities? Your work around the home? Your time spent with friends or loved ones? The things you do for fun? Your enjoyment of life?
- How many normal waking hours each day do you spend in a bed or chair?

**Day or Night Sweats**
- Do you experience sweating, particularly at night or in the evenings?
- Does this require you to change your sheets or clothing?
- Does this wake you up or impact your sleep?
- How often did this happen in the past month?

**Itching**
- Have you noticed changes in your skin, particularly itching?
- When you shower, do you ever feel itchy afterwards? How often?
- Have you found yourself taking shorter/fewer/cooler showers to try to avoid itchiness?
- What are other instances where you tend to feel itchy?

**Bone Pain**
- Have you felt any deep achiness throughout your body?
- Does bone pain ever cause you to change or limit your activities?

**HYPERVISCOSITY-RELATED SYMPTOMS**

**Concentration Problems**
- How often have you felt a “brain fog”—memory lapses (such as problems remembering words or dates), inability to pay attention for long periods, or generally having problems concentrating that interfere with your ability to work [or other relevant activity]?
- How has this impacted your life? Have you had to change school plans, work, or how you function at home?

**SPLENOMEGALY-RELATED SYMPTOMS**

**Abdominal Discomfort**
- Do you have abdominal discomfort, particularly after eating?
- Do you experience abdominal discomfort at any other time, for example, when lying down flat on your back?

**Early Satiety**
- Do you feel full quickly after meals?
- Are you losing weight, and if so, how much weight have you lost over the last 6 months?

*Weight loss and fever are cytokine-related symptoms that have also been observed in patients with PV and should be considered in a comprehensive symptom evaluation.*

Access a comprehensive patient counseling resource to use with your patients with PV at www.MPNConnect.com
Checklist for monitoring patients with MF

- **Assess the spleen** by palpation—and imaging (eg, ultrasound) if appropriate—at diagnosis

- Obtain a detailed picture of the patient’s symptom burden by asking open-ended questions about **specific symptoms known to be associated with MF**

- **Empower patients and caregivers** to take an active role in symptom identification by educating them about MF-related symptoms
Contextual questions to ask your patients with MF

Splenomegaly-Related Symptoms

**Early Satiety**
- Do you feel full quickly after meals?
- Have you lost weight in the past 6 months, without intentionally trying to?

**Abdominal Discomfort**
- Do you have abdominal discomfort, particularly after eating?
- Do you experience any dull or sharp pains in your abdomen?
- Do you experience abdominal discomfort at any other time?
- Do you find it difficult to get into a comfortable position for sleeping?

Cytokine-Related and Other Symptoms

**Fatigue and Inactivity**
- Do you feel tired even after getting enough sleep, or do you tire quickly during the day?
- How many normal waking hours each day do you spend in a bed or chair?
- Are there activities that you were able to do 3 months ago that you struggle with now?

**Concentration Problems**
- How often have you felt a “brain fog”—memory lapses (such as problems remembering words or dates), inability to pay attention for long periods of time, or generally having problems concentrating that interfere with your ability to work (or other relevant activity)?
- How has this impacted your life? Have you had to change school plans, work, or how you function at home?

**Day or Night Sweats**
- Do you experience sweating, particularly at night or in the evenings?
- Does this require you to change your sheets or clothing?
- Does this wake you up or impact your sleep? How often has it occurred in the past month?

**Bone Pain**
- Have you felt a dull achiness throughout your body (not just focused in one area or joint)?
- Do you feel achiness at night in bed or when sitting idle during the day?
- Does bone pain ever cause you to change or limit your activities?

**Itching**
- Have you experienced an increase in itchiness?
- When you shower, do you ever feel itchy afterwards? How often?
- Have you found yourself taking shorter/fewer/cooler showers to try to avoid itchiness?

Access a comprehensive patient counseling resource to use with your patients with MF at www.MPNConnect.com

*Weight loss and fever are cytokine-related symptoms that have also been observed in patients with MF and should be considered in a comprehensive symptom evaluation.
Online resources for patients with MPNs

Several organizations maintain online resources that may be useful for your patients with PV or MF. If asked for resources, consider sharing the following websites offering support, education, and awareness.

- Voices of MPN, an education and awareness initiative for patients, sponsored by Incyte (VoicesofMPN.com)
- Cancer Support Community (CancerSupportCommunity.org)
- CancerCare (CancerCare.com)
- Leukemia & Lymphoma Society (LLS.org)
- MPN Advocacy and Education International (MPNAdvocacy.com)
- MPN Education Foundation (MPNinfo.org)
- MPN Research Foundation (MPNResearchFoundation.org)
- National Institutes of Health (NIH.gov)
- National Organization for Rare Disorders (Rarediseases.org)

These organizations may have received funding or financial support from Incyte. They are independent groups and societies and their names are provided as a service and should not be considered an endorsement or imply an endorsement by Incyte.
References