Approach to the Diagnosis and Management of Essential Thrombocytosis in a Resource-Limited Setting

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ABSTRACT

Essential thrombocytosis (ET) is a myeloproliferative neoplasm (together with polycythemia vera, chronic myelogenous leukemia, and primary myelofibrosis) characterized by clonal proliferation of megakaryocytes, usually due to the presence of JAK2, CALR, or MPL mutations. Whereas a bone marrow aspirate and genetic testing for these mutations are necessary for an accurate diagnosis of ET, in resource-limited settings, these are often either inaccessible or limited by prohibitive costs. A nuanced clinical approach is necessary to diagnose and manage ET in these settings. In this study, we present a case of ET diagnosed and managed in a resource-limited rural setting in Kenya with hydroxyurea and aspirin. We highlight the importance of individualized therapeutic targets, the challenges with dose adjustments in the setting of hydroxyurea-induced neutropenia, and how extrapolated data from the use of hydroxyurea elsewhere may help guide such dose adjustments. Finally, we propose a rationalized approach to treating ET in a resource-limited clinical setting.

Keywords
Essential Thrombocytosis, Myeloproliferative Neoplasms, Hydroxyurea, Aspirin, Hydroxyurea-Induced Neutropenia, Vasomotor Symptoms, Thrombo-Hemorrhagic Complications, Kenya

INTRODUCTION

Essential thrombocytosis (ET), also called essential thrombocythaemia or primary thrombocythosis, is one of the myeloproliferative neoplasms (MPN) whose hallmark is the clonal proliferation of various myeloid cells with varying morphology, maturity, and efficiency. The other main MPNs are polycythemia vera (PV), chronic myelogenous leukemia (CML), and primary myelofibrosis (PMF) (Arber et al., 2016). ET is characterized by sustained megakaryocyte proliferation that leads to increased numbers of circulating platelets, often of various sizes (platelet anisocytosis). Figure 1, panel by Schafet et al., shows the appearance of ET on a peripheral blood film and on a bone marrow assay. (Tefferi & Pardanani, 2019). Approximately 85-90% of patients with MPNs will demonstrate mutually exclusive mutations in the JAK2 (60-65%), CALR (20-25%), or MPL (5%) genes (Cazzola & Kralovics, 2014; Klampfl et al., 2013; Nielsen et al., 2013). About 10-15% of patients have no such mutations (the so-called 'triple-negative') (Tefferi et al., 2014). ET constitutes approximately a third of all cases of MPNs in developed countries, with a median age at diagnosis of 60 years. Most patients enjoy a normal life expectancy, but survival is decreased in older patients and those with thrombotic complications (Hultcrantz et al., 2015; Roaldsnes et al., 2017; Srou et al., 2016; Tefferi & Barbui, 2017). The main features of ET include a persistently elevated platelet count of >450,000/µL on a complete blood count, a clinical course characterized by thrombotic and/or hemorrhagic events with a possible sphenomegaly, and marked thrombocytosis and hyperplasia of megakaryocytes on peripheral blood smear.

Figure 1: Histologic Features of Essential Thrombocythemia (Schafet, 2004)

In Panel A, a peripheral-blood smear from a patient with essential thrombocythemia contains an increased number of platelets, including giant platelets (arrow; Wright's stain, ×100). In Panel B, a specimen of bone marrow from a patient with essential thrombocythemia contains an increased number of megakaryocytes (hematoxylin and eosin, ×100). (Courtesy of Dr. Scott Murphy, American Red Cross Blood Services, Penn-Jersey Region, Philadelphia.)

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and bone marrow assays, respectively (Tefferi & Barbui, 2020). Asymptomatic patients with ET (about 50% of all cases) may be found when persistent thrombocytosis is noted on routine complete blood counts for other reasons. Disease-related symptoms of ET are largely vasomotor due to disturbances in microvascular circulations and include headaches, dizziness, fainting, blurring or transient loss of vision (e.g., amaurosis fugax, ocular migraines), non-specific fatigue, atypical chest pains, myalgias, acral paresthesia, erythromelalgias, and livedo reticularis, etc. (Wolanskyj et al., 2005). Patients may also present with complications related to thrombosis (due to both quantitative and qualitative plate dysfunctions) in various organs, e.g., strokes, acute coronary syndromes, superficial thrombophlebitis, deep vein thrombosis, pulmonary embolism, hepatic or portal vein thrombosis, digital ischemia, thrombosis-related first-trimester pregnancy losses, etc. (Tefferi & Barbui, 2017). Hemorrhagic manifestations tend to occur in cases of extreme thrombocytosis (platelet counts >1000,000/µL) as well as following treatment with high doses of non-steroidal anti-inflammatory drugs (Bellucci et al., 1986; Landolfi et al., 2006). Treatment of ET is based on individualized stratification of the risks and/or occurrence of thrombosis or bleeding (Barbui et al., 2015) and generally includes observation and cytoreductive therapy with medications such as low-dose aspirin and hydroxyurea (first-line therapy) (Rocca et al., 2020; Tefferi & Barbui, 2020). Interferon alfa, anagrelide, ruxolitinib, and apheresis may be used as second-line agents (Birgégård, 2016; Tefferi & Barbui, 2020). Older agents like busulphan and phosphorus-32 (32P) may also be used as second-line agents but have been associated with increased risks of acute myelogenous leukemia (Finazzi et al., 2005; Tefferi & Barbui, 2020).

CASE SUMMARY

History and Physical Examination

A 60-year-old married father of three adults, a tailor by profession from Pipeline Estate, Nakuru County, Kenya, with no preceding significant medical history, first presented to us in February 2022, with concerns of pain and darkish discoloration of the small left toe. This was associated with a ≥6-month’ history of bilateral lower limb numbness, paresthesia, and burning pain of both hands and feet in a stocking-and-gloving distribution. He’d also experienced recurrent global headaches, blurring of vision, occasional dizziness, myalgias, general fatigue, reduced effort tolerance, and mild bipedal edema. However, he had no history to suggest heart failure, bleeding diatheses, stroke-like symptoms, or deep venous thrombosis. He had no known family history of any hematological or cardiovascular diseases. The rest of the systemic inquiry was unremarkable.

On examination, he was in fair general health. His lower limb examination revealed multiple macular-to-patchy non-tender, non-blanching discrete skin lesions on both legs and thighs, mild bilateral pitting ankle edema, with the left small toe appearing remarkably darkened but non-tender, and with an associated septic wound on its tip. The neurovascular exam of both legs as well as the rest of the musculoskeletal exam were normal. He had no features of chronic liver disease but had a dull percussion note over Traube’s space, indicating splenomegaly. A full neurological exam only showed mild impairment in the peripheries of light touch and vibration, while examination of the other systems was unremarkable.

Diagnostic Evaluation

During that first encounter, it was noted on a complete blood count that his total platelet count was markedly elevated at 2306 x10^3/μL (the normal range is 150-450 x10^3/μL), while the total leucocyte count and hemoglobin were both normal at 10.4 x10^3/μL and 14 g/dl, respectively. He had normal random blood glucose, normal renal and liver panels, a negative HIV rapid test, a negative COVID-19 rapid antigen test, a normal chest x-ray and electrocardiogram, and a normal erythrocyte sedimentation rate of 8 mm/hr. Ultrasonography showed a mild splenomegaly of 14cm and early bilateral leg varicose veins, but no deep venous thrombosis. He was assessed to have features of a possible underlying myeloproliferative disorder, predominantly of the ET phenotype. He got lost to follow-up until nine months later, when he re-presented with a worsening of similar symptoms. His platelet count had further increased to 2733 x10^3/μL. A peripheral blood film showed extreme thrombocytosis with both giant and small platelets, consistent with primary (essential) thrombocytosis. Due to severe financial and logistical challenges, it was impossible to do a bone marrow aspirate or any genetic tests.

Management and Follow-Up

His clinical syndrome was most consistent with ET, with predominant vasomotor symptoms and associated sensory peripheral neuropathy. He was put on oral hydroxyurea (HU) starting at a dose of 1g daily and aspirin at 75mg daily. For the neuropathy, he was put on pregabalin 75mg daily (and amitriptyline 25mg nocte was later added during follow-up). The septic wound was surgically managed to full healing. While on HU, he developed symptomatic hyperuricemia due to HU-induced platelet degradation (with a clinical syndrome of non-tophaceous acute gouty polyarthritis), which was successfully managed with allopurinol and analgesics. Besides, the dose of HU was adjusted to a maximum tolerable dose of 1.5 g/day, aiming to keep an absolute neutrophil count of ≥1.5 x10^3/µL. Significantly, whenever his absolute neutrophil count reduced to <1.5 x10^3/µL, he developed a recurrent triad of oropharyngeal candidiasis, septic grade 2 tonsillitis, and cytisitis. This was fully treated with antimicrobials and supportive therapy. The HU in each case was stopped for a week and subsequently restarted at a much lower dosage, resulting in the resolution of the neutropenia and the recovery of the target absolute neutrophil count. However, the platelets
and the uric acid levels rose precipitously when HU was stopped (or dosage reduced), with a corresponding recurrence of mild-to-moderate vasomotor symptoms and gouty polyarthritis. These have been fully controlled with a corresponding adjustment of the various drug dosages. He is currently on follow-up at the medical clinic with ongoing clinical and laboratory monitoring to target the individualized therapeutic goals described earlier and clinical surveillance for infections, transformation to other MPNs, and any adverse effects of the various drugs. Table 1 below shows a composite summary of his complete blood count, uric acid levels, and relevant interventions.

### Table 1: Summary of the Complete Blood Count, Uric Acid Levels, and Interventions

<table>
<thead>
<tr>
<th>Date</th>
<th>Total Platelets</th>
<th>Total WBC</th>
<th>Hemoglobin</th>
<th>Uric acid</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/2/2022</td>
<td>2306</td>
<td>10.4</td>
<td>14.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>15/11/2022</td>
<td>2733</td>
<td>11.4</td>
<td>11.7</td>
<td>2.3</td>
<td>HU 1g + ASA 75mg OD started</td>
</tr>
<tr>
<td>22/11/2022</td>
<td>2472</td>
<td>10.9</td>
<td>12.1</td>
<td>-</td>
<td>HU 1g + ASA 75mg OD</td>
</tr>
<tr>
<td>2/12/2022</td>
<td>2124</td>
<td>9.7</td>
<td>12.0</td>
<td>13.2</td>
<td>HU 1.5g + ASA 75mg + ALP 100mg OD</td>
</tr>
<tr>
<td>29/12/2022</td>
<td>942</td>
<td>7.0</td>
<td>12.4</td>
<td>7.9</td>
<td>HU 1.5g + ASA 75mg + ALP 200mg OD</td>
</tr>
<tr>
<td>27/1/2023</td>
<td>918</td>
<td>3.6(N=67%, ANC=2412/µL, L=28%)</td>
<td>12.3</td>
<td>12.9</td>
<td>HU 1.5g + ASA 75mg + ALP 300mg OD</td>
</tr>
<tr>
<td>10/3/2023</td>
<td>745</td>
<td>3.1(N=64%, ANC=1984/µL, L=28%)</td>
<td>13.0</td>
<td>4.6</td>
<td>HU 1.5g + ASA 75mg + ALP 300mg OD</td>
</tr>
<tr>
<td>5/5/2023</td>
<td>675</td>
<td>2.2(N=63%, ANC=1386/µL, L=31%)</td>
<td>12.6</td>
<td>3.0</td>
<td>HU 1g + ASA 75mg + ALP 100mg OD + Abx</td>
</tr>
<tr>
<td>3/7/2023</td>
<td>977</td>
<td>2.6(N=59%, ANC=1534/µL, L=34%)</td>
<td>13.3</td>
<td>4.6</td>
<td>HU 1.5g + ASA 75mg + ALP 100mg OD</td>
</tr>
<tr>
<td>14/8/2023</td>
<td>673</td>
<td>2.8(N=57%, ANC=1596/µL, L=38%)</td>
<td>13.4</td>
<td>4.0</td>
<td>HU 1.5g + ASA 75mg + ALP 100mg OD</td>
</tr>
<tr>
<td>11/9/2023</td>
<td>535</td>
<td>2.5(N=59%, ANC=1475/µL, L=30%)</td>
<td>13.0</td>
<td>3.5</td>
<td>HU 0.5g + ASA 75mg + ALP 100mg OD + Abx</td>
</tr>
<tr>
<td>9/10/2023</td>
<td>1445</td>
<td>4.0</td>
<td>13.0</td>
<td>8.6</td>
<td>HU 1g + ASA 75mg + ALP 200mg OD</td>
</tr>
<tr>
<td>8/11/2023</td>
<td>899</td>
<td>3.8(N=63%, ANC=2394/µL, L=31%)</td>
<td>12.7</td>
<td>2.5</td>
<td>HU 1.5g + ASA 75mg + ALP 200mg OD</td>
</tr>
</tbody>
</table>

Key: Note the adjustment of HU dosages whenever the absolute neutrophil count dropped below 1500/µL, and the subsequent precipitous increase in platelet counts and uric acid levels

#### RESULTS AND DISCUSSION

A diagnostic evaluation of suspected ET includes a medical history focused on the occurrence of thrombotic and hemorrhagic manifestations, with a careful search for concomitant cardiovascular risk factors in the setting of thrombotic complications. The diagnostic criteria of ET by the World Health Organization and the International Consensus Classification (Arber et al., 2022) require either all four of the major criteria or the first three major criteria plus the minor criterion, as shown in Table 2 below.
In our patient, it was not possible to do a bone marrow aspiration and trephine biopsy (BMAT) or any genetic tests for JAK2, CALR, or MPL mutations due to severe financial challenges. These services are not readily available in the vast majority of our health centers, and their access upon referrals to regional reference laboratory centers is severely hindered by their prohibitive costs.

The main differential diagnosis for ET is reactive thrombocytosis (RT). Platelets are also members of the acute phase reactant superfamily, which will be elevated in many inflammatory and other conditions, e.g., infections, iron deficiency anemia, acute bleeding, trauma, asplenia, etc. Patients with RT will have evidence of these conditions as well as elevation of other acute phase reactants (e.g., C-reactive protein, erythrocyte sedimentation rate, ferritin, etc.). (Schafer, 2004). Other MPNs must also be excluded prior to initiating treatment for ET. In our patient, a targeted clinical evaluation ruled out alternative diagnoses. He had no features of inflammation or trauma; he had a normal ESR; he maintained a persistently normal leucocyte count (pretreatment) and normal hemoglobin; and his platelets were too high to be compatible with just a RT. A validated simple laboratory scoring system based on a complete blood count that distinguishes ET from RT is consistent with our assessment of ET in this case (Shen et al., 2021).

At any rate, one would expect massive splenomegaly with CML (and severe leukocytosis) and PMF (and severe anemia), while PV would have marked polycythemia.

The goals of treatment in ET are to alleviate vasomotor symptoms, reduce the complications related to thrombosis and/or hemorrhage, and control splenomegaly (if present). Decisions on therapeutic choices are based on individual risk stratification and the availability and tolerability of the various agents. Low-dose aspirin (40-100 mg orally administered once daily) and HU (at 15 mg/kg/day orally administered at a usual starting dose of 500mg once or twice daily) are first-line agents (Tefferi & Barbui, 2020). Aspirin can reduce vasomotor symptoms and thrombo-hemorrhagic complications in most cases of ET. Higher doses are associated with increased risks of gastritis and gastrointestinal bleeding. HU is effective in reducing platelet counts, controlling splenomegaly, and reducing vasomotor symptoms in ET. The dose of HU is adjusted to a target platelet count of 100,000-450,000/µL while limiting leukocytopenia and anemia by doing weekly-to-monthly complete blood count monitoring (Tefferi & Barbui, 2020). The response rates of HU vary from about 80% complete response to 15% partial response using the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-NRT) and the European LeukemiaNet (ELN) criteria (Hernández-Boluda et al., 2011). Adverse effects of HU include oral ulcers, skin rashes, hyperpigmentation, long-term lung and liver toxicities, etc. HU is contraindicated in pregnancy and lactation. HU-induced neutropenia due to myelosuppression may manifest as recurrent infections presenting with fever, sore throat, urinary tract infections, etc. (Antonioli et al., 2012; Luchtmann-Jones et al., 2016). These effects are reversible by withholding HU for 1 to 2 weeks and then re-initiating at a lower dosage (Wang et al., 2011). When our patient got recurrent HU-induced neutropenia-related infections, the HU was withheld for one week in each case and successfully re-started at lower dosages tailored to therapeutic targets.

There are no studies that specifically address the modification of doses of HU for ET in cases of severe HU-induced neutropenia. However, extrapolation of expert consensus recommendations from the use of HU in sickle cell anemia in children may give guidance on the definition of HU-related myelosuppression and toxicities, as well as dose adjustments to the maximum tolerated dosages (MTD) in such cases (McGann et al., 2016; McGann & Ware, 2015). This is demonstrated in Table 3 below.

Based on these recommendations, an absolute neutrophil count of ≥1500/µL was adopted for our patient as the target for defining the maximum tolerated dosage of the HU, with the uppermost dosage of 1.5 g/day. So far, the recommended target platelet count of 100,000-450,000/µL while on HU treatment has not been achieved due to the concurrence of HU-related neutropenia, as highlighted.

Table 2: WHO diagnostic criteria for Essential Thrombocythemia (Arber et al., 2022)

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Platelet count ≥450 × 10⁹/L</td>
</tr>
<tr>
<td>2. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyper-lobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers</td>
</tr>
<tr>
<td>3. Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms</td>
</tr>
<tr>
<td>4. Presence of JAK2, CALR, or MPL mutation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis</td>
</tr>
</tbody>
</table>

**Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion.**

Key: CML: chronic myeloid leukemia; ET: essential thrombocythemia; PMF: primary myelofibrosis; PV: polycythemia vera; WHO: World Health Organization.
Interestingly, the patients’ subjective symptoms have almost completely resolved on HU and aspirin. Therefore, in resource-limited clinical settings, we propose a practical and rational approach to the diagnosis and treatment of ET, as summarized in the algorithm shown in Table 4 below.

### Table 3: Hematological parameters used to define the hydroxyurea maximum tolerated dose (MTD) with mild marrow suppression (McGann et al., 2016; McGann & Ware, 2015)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Toxicity criteria</th>
<th>Escalation criteria</th>
<th>Target MTD value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute neutrophil count (ANC, x 10^9/l)</td>
<td>&lt; 1.0</td>
<td>&gt; 3.0</td>
<td>1.5–3.0</td>
</tr>
<tr>
<td>Absolute reticulocyte count (ARC, x 10^9/l)</td>
<td>&lt; 80 (unless Hb ≥ 9.0)</td>
<td>&gt; 200</td>
<td>100–200</td>
</tr>
<tr>
<td>Platelets (x 10^9/l)</td>
<td>&lt; 80</td>
<td>&gt; 150</td>
<td>&gt; 80</td>
</tr>
<tr>
<td>Hemoglobin (Hb gm/dl)</td>
<td>Hb &lt;4.0 or Hb &lt;6.0 unless ARC &gt;100</td>
<td>&gt; 6.5</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: An Algorithm for the Diagnosis and Management of Essential Thrombocytosis in a Resource-Limited Setting

#### A. Platelet count: 450-1000 x 10^3/µL
1. Rule out RT: inflammatory conditions, trauma, iron deficiency anemia, etc., elevated CRP, ESR, procalcitonin, and other acute phase reactants.
2. If no evidence of RT, go to B.

#### B. Platelet count: >1000 x 10^3/µL
1. Clinically: vasomotor symptoms, thrombotic and/or hemorrhagic complications.
2. Peripheral blood film: presence of marked/severe/extreme thrombocytosis with platelet anisocytosis.
3. Clinically rule out other MPNs using a complete blood count, targeted clinical examination, and peripheral blood film.
4. Bone marrow aspirate and trephine biopsy, where possible: findings meeting the major criteria for ET diagnosis.
5. Make a presumed or definitive diagnosis of ET and go to C.

#### C. Diagnosis of ET
1. Start on low-dose aspirin and hydroxyurea.
2. Therapeutic target platelet counts of 150-450 x 10^3/µL, and an absolute neutrophil count of ≥ 1.5 x 10^9/µL.
3. Individualize therapeutic targets.
4. Monthly follow-ups with complete blood counts (and any other relevant tests).
5. Monitor for therapeutic targets, drug adverse effects, and disease transformations (e.g., into leukemias).

**Key:** ET=essential thrombocytosis, RT=reactive thrombocytosis, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, and MPNs=myeloproliferative neoplasms.

### CONCLUSION
In resource-limited settings, a diagnosis of ET must still be made through a high index of suspicion and a nuanced approach that incorporates compatible clinical features, persistent thrombocytosis (especially with platelet counts >1000 x 10^3/µL), and a simple peripheral blood smear that shows extreme thrombocytosis with platelet anisocytosis. This is followed by a meticulous, targeted evaluation to rule out reactive thrombocytosis and other MPNs. A BMAT biopsy and genetic testing for JAK2, CALR, or MPL mutations are ideally required for proving a diagnosis of ET, but in resource-limited settings, obtaining these tests is usually hopelessly vetoed by their inaccessibility and prohibitive costs. HU and aspirin are widely available in most clinical settings and should judiciously be used to treat ET with careful monitoring based on individualized treatment targets.

### RECOMMENDATIONS
HU-induced neutropenia is a dose-limiting adverse effect of HU therapy that may complicate ET treatment and hinder the attainment of target platelet levels. Unfortunately, no robust data currently exists in the literature that would give guidance on dose adjustments in such cases. More clinical trials and expert consensus recommendations are necessary to bridge this gap, especially with a focus on resource-limited clinical contexts.

### Acknowledgement
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### REFERENCES


