HEMATOLOGICAL MANIFESTATIONS IN HIV INFECTION

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INTRODUCTION

HIV was first recognized more than 27 years ago, and since then it has reached pandemic proportions. Within 2 decades, more than 50 million people have been infected with the human immunodeficiency virus (HIV) and 20 million have died. Worldwide, two-thirds of the 36 million known carriers of HIV are living in sub-Saharan Africa.

The overall risk of anesthesia and surgery in HIV Positive patient needs further study. Twenty to 25% of HIV-positive patients will require surgery during their illness. Anesthesiologists need to be aware of the disease when deciding on the course of anesthesia.

This multi organ disease may be complicated either by opportunistic infections, tumors, substance abuse, or antiretroviral therapeutic drugs, which all can have an impact on anesthesia.

Hematologic Manifestations of HIV Infection

Shortly after the first description of AIDS, cytopenias of all major blood cell lines were increasingly recognized among patients infected with the HIV.

In one early series of patients with AIDS;
- Anemia was noted in approximately 70%.
- Lymphopenia was noted in 70%.
- Neutropenia was noted 50%.
- Thrombocytopenia was noted in 40%.
THROMBOCYTOPENIA

Epidemiology
Thrombocytopenia was first associated with AIDS before the discovery of the HIV.1 Prior to the use of highly active antiretroviral therapy (HAART), HIV-associated thrombocytopenia (HIV-CITP, platelet count < 150 \( \times 10^9 \) /L) was identified in approximately 5% to 30% of patients infected with HIV-1.2-5.

A review of the medical records of 36,515 patients infected with HIV who were participants in the Multistate Adult and Adolescent Spectrum of Disease Project reported a 1 year incidence of thrombocytopenia of 3.7%, (defined as a platelet count of less than 50 \( \times 10^9 \) /L\(^{-1}\)). The incidence and severity of thrombocytopenia was associated with the stage of disease with an incidence of 1.7% among patients with HIV infection, but not clinical or immunologic AIDS, 3.1% among persons with immunologic AIDS (CD4 lymphocytes < 200/µL) and 8.7% in patients with clinical AIDS.5

By logistic regression analysis sever thrombocytopenia (platelet count 50x10\(^9\) /L) associated with;

• clinical AIDS.
• CD4 lymphocyte count of < 200/µL.
• age > 45 years.
• Intravenous drug use.
• Lymphoma and/or anemia.

The causes of thrombocytopenia in HIV-infected patients can be divided into two groups: primary HIV-associated thrombocytopenia and secondary thrombocytopenia.

Primary HIV-associated thrombocytopenia
PHAT is the major cause of thrombocytopenia HIV-infected patients. Clinically, PHAT is similar to classic idiopathic thrombocytopenic purpura (ITP) except that;

• Splenomegaly is more commonly noted in patients with PHAT than in ITP.
• Platelet counts are often higher in HIV-infected patients.
• Mild thrombocytopenia occasionally resolves without therapy.\(^6\)-\(^{10}\)
1. Aetiology

It is complex, bone marrow examination, as in classic ITP, reveals normal or increased numbers of megakaryocytes in the face of reduced numbers of circulating platelets. This combination suggests the presence of ineffective platelet production and/or increased peripheral destruction.

Kinetic studies using radiolabeled autologous platelets from HIV-infected individuals have shown that both factors contribute: there is more than a 50% reduction in platelet survival and a 50% reduction in platelet production.11

In a comprehensive study comparing the kinetics of the megakaryocyte-platelet system in HIV-infected thrombocytopenic patients with normal controls, the following differences were found.12

- Reduced platelet survival (87 versus 232 hours)
- Reduced recovery of infused platelets (33 versus 65%)
- Increased megakaryocyte number [30 x 10(6) versus 11 x 10(6)/kg]
- Reduced marrow megakaryocyte progenitors [3.3 versus 27 CFU-Meg/1,000 CD34(+) cells]
- Increased endogenous thrombopoietin (TPO) concentration (596 versus 95 pg/mL) and increased TPO receptor number (461 versus 207 receptors/platelet).

These studies indicate a triad of shortening of platelet life span by two-thirds, a doubling of splenic platelet sequestration, and ineffective delivery of viable platelets, despite a threefold expansion in marrow megakaryocyte mass driven by TPO.

a. Reduced platelet survival

Peripheral destruction of platelets in patients with PHAT is probably due to the presence of antiplatelet antibodies in the serum and on the surface of platelets3,13. Platelet-associated IgG cross reacts with the platelet glycoprotein complex (GP)IIb/IIIa and the HIV envelope glycoproteins GP160/12015.

IgM antiidiotype antibodies directed against platelet anti-GPIIIa appears to directly regulate the degree of thrombocytopenia21. In addition, anti-HIV antibodies that bind to normal control platelets were found in 50% of sera from patients with PHAT as compared with only 5 percent of sera from HIV-infected patients with normal platelet counts,19 these suggest that molecular mimicry between HIV proteins and platelet GPIIb/IIIa may be important in the pathogenesis of PHAT.22
Macrophages in the reticuloendothelial system (primarily splenic) are the major mediators of platelet destruction, binding to the Fc receptors on antibody- or immune complex-bound cells and eliminating them through phagocytosis.\textsuperscript{23,24}

b. Ineffective platelet production
HIV transcripts in the megakaryocytes of patients with PHAT, and it is directly able to infect platelet progenitor cells\textsuperscript{25-27}. Electron microscopy of megakaryocytes from HIV-infected individuals with thrombocytopenia clearly demonstrates ultrastructural abnormalities not encountered in noninfected patients;

- Blebbing of the surface membrane.
- Vacuolization of peripheral cytoplasm which is more common\textsuperscript{2}

Infection of these platelet precursors impairs subsequent development and maturity, leading to the observed reduction in platelet production. Other alterations in the bone marrow microenvironment may also contribute to poor platelet production \textsuperscript{28-29}. Increased programmed cell death (apoptosis) of bone marrow megakaryocytes in HIV-infected patients has also been postulated as a contributor to thrombocytopenia.

2. Treatment of PHAT
After the exclusion of secondary causes of thrombocytopenia and discontinuation of potentially marrow-suppressing medications, there are many therapies available for the management of PHAT.

Individual circumstances dictate the necessity and acuity of therapy, as a result, therapeutic decisions should be made on a case-by-case basis, considering:

- The patient's current platelet count
- The potential toxicities of therapy
- Other co-morbid conditions that increase the risk of bleeding complications (e.g., hemophilia, metastatic malignancy)
- A spontaneous remission rate of almost 20% in patients with PHAT.\textsuperscript{34}

a. Zidovudine
Zidovudine (AZT) has been the mainstay of therapy of PHAT, despite its well-recognized potential for suppression of myeloid and an erythroid precursor, AZT increases platelet production in kinetic studies of HIV-infected individuals.\textsuperscript{11} The platelet count increases by more than 50,000/µL after eight weeks of AZT therapy (2 g/day for two weeks followed by 1 g/day for six weeks)\textsuperscript{36}. 

b. **HAART**
HAART may also be associated with improvement in PHAT as it reduces complications of HIV infection, including the occurrence of opportunistic infections and Kaposi’s sarcoma.

c. **Intravenous Immune Globulin**
Intravenous immune globulin (IGIV, IVIG) produces dramatic, rapid improvements in platelet counts in the majority of patients with PHAT.

A review of published cases described platelet counts exceeding 50,000/microL in almost 90 percent of patients after a single treatment with high-dose IGIV. (1 to 2 g/kg), IGIV is thought to saturate Fc receptors in the reticuloendothelial system, thereby preventing the destruction of platelets (and red blood cells) coated with antibodies or immune complexes.

The response seen after therapy is typically transient and multiple repeated administrations may be required. In addition, the high cost, long infusion time (four to five hours), and limited supply of human immunoglobulin reduce the overall utility of this therapy for long-term management.

Intravenous immunoglobulins remain a treatment of choice in situations requiring the rapid correction of low platelet counts, such as anticipated surgery or as an adjuvant to platelet transfusion during acute bleeding episodes.

d. **Anti-D immunoglobulin**
A component of IGIV, anti-Rh (D) (anti-D, WinRho™), is effective only in non-splenectomized, Rh-positive patients in whom the immunoglobulin binds to the erythrocyte D antigen. These sensitized erythrocytes undergo immune-mediated clearance by the reticuloendothelial system. By competitively binding Fc receptors in the spleen, these anti-D-bound erythrocytes help reduce the destruction of antibody-coated platelets, thereby increasing circulating platelet counts. It is an effective alternative to IGIV in patients with PHAT, less expensive than high dose IGIV, and can be given within short infusion time. (Few minutes)

e. **Corticosteroids**
Corticosteroids have demonstrated efficacy in HIV-associated thrombocytopenia; Prednisone (1mg/kg/day) improves platelet counts and decreases incidence of bleeding after 3 weeks, however the risk of steroid-associated side effects is significant (clinical sequelae, including weight gain, cushingoid faces, oral candidiasis, dysphoria, acne, reactivation herpes simplex virus and proximal myopathy)
f. **Interferon alfa**

Interferon alfa is another option for the management of chronic PHAT. Three million units of interferon-alfa increase mean platelet counts more than fivefold within four weeks.

g. **Vincristine**

There is limited experience with vincristine in PHAT. It is effective in patient with Kaposi’s sarcoma, the increase in platelet sustains for more than 6 months.

h. **Splenectomy**

Patients with persistent thrombocytopenia or dependence on repeat IGIV or anti-D infusions may benefit from splenectomy, mean platelet counts are increase significantly immediately after splenectomy in 68 patients; a sustained response after six months was noted in 82 percent.

i. **Splenic irradiation**

It is less commonly employed than splenectomy, it is another option for patients don’t respond to standard interventions or those considered poor surgical candidates, the main disadvantage of splenic irradiation is a short duration of response.

j. **Thrombopoietic growth factors**

Patients with PHAT, as compared with healthy control subjects, have markedly elevated levels of endogenous thrombopoietin (mean levels of 596 versus 95 pg/mL) and increased thrombopoietin receptor numbers (461 versus 207 receptors/platelet). The role of eltrombopag and other thrombopoietin receptor agonists in the management of PHAT has not been clearly defined.

3. **Secondary causes of thrombocytopenia**

Secondary causes of thrombocytopenia are generally the result of underlying opportunistic infections, malignancy, and co-morbid conditions resulting in hypersplenism (table 1).
### Causes of Thrombocytopenia HIV

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Bacterial: Bartonellosis, Bacteremia/sepsis, Ehrlichiosis; Parasitic: Toxoplasma, Babesia; Mycobacterial: Disseminated tuberculosis, Disseminated mycobacterium avium-complex; Viral: Cytomegalovirus, HIV, Rubella; Fungal: Histoplasmosis, Coccidioidomycosis, Other disseminated fungal infections</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Kaposi's sarcoma, Metastatic adenocarcinomas, Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Secondary hypersplenism</td>
<td>Chronic viral hepatitis/cirrhosis, Other causes of hepatitis/cirrhosis</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td></td>
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<tr>
<td>Disseminated intravascular coagulation</td>
<td></td>
</tr>
</tbody>
</table>

Patients with HIV infection may be more susceptible to certain medication-associated thrombocytopenias, as an example, higher frequency of heparin-induced thrombocytopenia (HIT) among heparin-exposed patients with HIV.31
Platelet Function and HIV

In vitro, platelet aggregation is induced by agonists such as adrenaline, thrombin receptor-activating peptide (TRAP), ADP and collagen.

These agonists are used to assess platelet function in many different assays. TRAP, ADP and collagen stimulate platelet aggregation by binding to platelet-surface receptors [protease activated receptor 1 (PAR-1), P2Y1/P2Y12 and glycoprotein VI (GPVI)/α2β1, respectively], resulting in a series of intracellular changes, including phospholipase mediated alterations in intracellular calcium and protein phosphorylation, adrenaline stimulates platelet aggregation indirectly by acting on platelet α2- adrenergic receptors to augment the aggregation effect of other platelet agonists.

Aggregation-specific platelet function analysers measure platelet aggregation upon exposure to either a narrow range of agonists or a single agonist at a single concentration, thus do not reflect the complex biological environment of different disease states.

A case–control study of platelet reactivity in 20 HIV-infected (HIVpos) and 20 age and sex-matched HIV-negative (HIVneg) individuals.

Time-dependent platelet aggregation was measured in response to increasing concentrations of platelet agonists: epinephrine, collagen, thrombin receptor activating peptide and ADP using light absorbance.

Evaluation of dose–response curves revealed multiple differences in platelet aggregation between the HIVpos and HIVneg groups; Platelet aggregation was decreased in the HIVpos group as compared with the HIVneg group in response to TRAP, ADP and collagen and increased in the HIVpos group as compared with the HIVneg group in response to adrenaline.
1. **Adrenaline**
Platelet from the HIVpos group exposed to adrenaline were more reactive, with a horizontal shift in the curve (Fig 1 a), significantly lower mean adrenaline concentration was required to induce 50% platelet aggregation.

![Graph showing adrenaline effect on platelet aggregation](image)

**logEC50 difference, \( P = 0.03 \)**

2. **Thrombin receptor-activating peptide**
Exposure to TRAP in HIVpos group induced significantly less platelet aggregation at maximal and submaximal concentration.

![Graph showing TRAP effect on platelet aggregation](image)

% aggregation difference at
- 10 \( \mu \text{M}, \ P = 0.011 \)
- 20 \( \mu \text{M}, \ P = 0.012 \)
3. **ADP**
Exposure to submaximal concentration of ADP also resulted in significantly less platelet aggregation in the HIVpos group (Fig 1c).

4. **Collagen**
Exposure to submaximal concentration of collagen resulted in significantly less aggregation in HIVpos group. (Fig 1d)
Regional Anesthesia and ITP

Spinal hematoma after neuraxial techniques in modern anesthetic practice is rare. The frequency of spinal hematoma in the large (>1000 subjects) recent studies (1995–present) ranges from 0 to 3.70:10,000 and varies considerably depending on the surgical indication, particularly with respect to the obstetric (0–0.20:10,000) versus the non-obstetric population (0 –3.7:10,000). In spite of this it remains one of the most feared complications, mostly because of its potential for irreversible injury and partly because it may be minimized with close attention to modifiable risk factors, (thromboprophylaxis, traumatic needle insertion and known coagulopathies).

However, there is a paucity of data in the literature regarding the provision of neuraxial techniques in patients with the most common bleeding diatheses.

In systemic review 14 articles, were published between January 1, 1975 and October 1, 2008. 325 patients with ITP underwent a total of 326 neuraxial techniques.

Of 326 neuraxial techniques, 324 were in the obstetric population, (282 lumbar epidural anesthetics, 41 spinal anesthetics, 2 paravertebral blocks, and 1 thoracic epidural anesthetic were placed in the setting of ITP.

The perioperative management of neuraxial techniques in ITP varied considerably among the 14 source articles (Table 2). The diagnosis of ITP was known before the block in all but three instances in which the low platelet count was revealed on review of the complete blood count after lumbar epidural analgesia had been initiated.
## Table (2) Data Summary of Neuraxial Techniques in the Setting of Idiopathic Thrombocytopenic Purpura (ITP)

<table>
<thead>
<tr>
<th>Author/reference</th>
<th>Population/N</th>
<th>No. of blocks</th>
<th>Preblock platelet count (x 10^9 L^-1)</th>
<th>Treatment</th>
<th>Gauge/type</th>
<th>Difficult insertion</th>
<th>Outcome</th>
<th>Authors' recommendations</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td>Lumbar epidural</td>
<td>OB N = 19</td>
<td>19</td>
<td>Plt &lt;100 (N = 6)</td>
<td>Steroids (N = 12)</td>
<td>N/A</td>
<td>N/A</td>
<td>No complications</td>
<td>Plt &lt;100 not contraindicated to ETN</td>
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<td></td>
<td></td>
<td></td>
<td>Plt = 100-150 (N = 15)</td>
<td>IVig (N = 2)</td>
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<td>Both (N = 9)</td>
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<td>Plt = 61-100 (N = 13)</td>
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<tr>
<td>Frank et al.</td>
<td>OB N = 350</td>
<td>155</td>
<td>Plt &lt;50 (N = 2)</td>
<td>Transferred to Plt &gt;50</td>
<td>N/A</td>
<td>N/A</td>
<td>No complications</td>
<td>Decision must be made on case-by-case basis</td>
<td>ITP included ETN, CT, prechamplasia Epidual catheter removed if Plt &gt;60</td>
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<td></td>
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<td>Plt = 51-60 (N = 2)</td>
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<tr>
<td>Raimos et al.</td>
<td>OB N = 30</td>
<td>10</td>
<td>Plt &gt;100 (N = 5)</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>No complications</td>
<td>None</td>
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<td></td>
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<td></td>
<td>Plt = 70-100 (N = 5)</td>
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<tr>
<td>Modell-Sheizman et al.</td>
<td>OB N = 1</td>
<td>1</td>
<td>Plt = 26</td>
<td>18-G Tuohy, 20-G Catheter</td>
<td>No</td>
<td>No complications</td>
<td>None</td>
<td>ITP undiagnosed before birth, Platelet count determined after placement of Velocath. Exclusion criteria for epidural not indicated</td>
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<tr>
<td>Weber et al.</td>
<td>OB N = 42</td>
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<tr>
<td>Frolich et al.</td>
<td>OB N = 1</td>
<td>1</td>
<td>Plt = 61</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
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<td>None</td>
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<td></td>
<td>OB N = 1</td>
<td>3</td>
<td>Plt = 69.96</td>
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<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Sweeny et al.</td>
<td>OB N = 1</td>
<td>1</td>
<td>Plt = 73</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>No complications</td>
<td>None</td>
<td>TEG analysis normal</td>
</tr>
<tr>
<td></td>
<td>OB N = 1</td>
<td>1</td>
<td>Plt = 2</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>No complications</td>
<td>None</td>
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<tr>
<td>Ramaas et al.</td>
<td>OB N = 64</td>
<td>6</td>
<td>Plt = 13-15</td>
<td>None</td>
<td>17-G Tuohy</td>
<td>N/A</td>
<td>No complications</td>
<td>None</td>
<td>LEA safe if Plt &gt;100</td>
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<td>Thoracic epidural</td>
<td>OB N = 61</td>
<td>61</td>
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<td>19-G Catheter</td>
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<td>Plt = 126-149 (N = 41)</td>
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<td>Kong et al.</td>
<td>OB N = 64</td>
<td>6</td>
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<td>17-G Tuohy</td>
<td>N/A</td>
<td>No complications</td>
<td>None</td>
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<tr>
<td>Spinal</td>
<td>OB N = 39</td>
<td>35</td>
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<td>Transferred to Plt &gt;50</td>
<td>N/A</td>
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<td>Decision must be made on case-by-case basis</td>
<td>ITP included ETN, CT, prechamplasia</td>
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<td>Raimos et al.</td>
<td>OB N = 7</td>
<td>7</td>
<td>Plt &gt;100 (N = 2)</td>
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<td>22G or 29G Whistler or Yale</td>
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<td>No complications</td>
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<td>Plt = 70-100 (N = 5)</td>
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<td>Chang et al.</td>
<td>OB N = 45</td>
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<td>Plt = 101 (N = 2)</td>
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<td>29G</td>
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<td>No complications</td>
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<td>None</td>
<td>29G</td>
<td>Type N/A</td>
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<td>Type N/A</td>
<td>No complications</td>
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</table>

*Numeric values presented as x 10^9 L^-1.

OB = obstetric; G = needle gauge; CT = gestational thrombocytopenia; CYN = gynecologic; IVig = Intravenous immune globulin; ITP = idiopathic thrombocytopenic purpura. LEA = lumbar epidural anesthesia; ETN = number of patients; N/A = data not indicated in reference; ETN = neuraxial technique; Plt = platelets; TEG* = thromboelastography.

4 In the largest case series by Frank et al., there were 170 patients (135 LEA, 35 spinal blocks) with ITP, CT, and Pnechamplasia. The authors did not enumerate each entity.
Interestingly, three articles (i.e., ITP was undiagnosed before neuraxial technique) reported the lowest platelet counts before needle insertion among all 14 source articles: $2 \times 10^9 \text{L}^{-1}$, $18 \times 10^9 \text{L}^{-1}$, and $26 \times 10^9 \text{L}^{-1}$. The authors of 10 of the 14 source articles did not seek to treat the thrombocytopenia before needle insertion. When the diagnosis of ITP was established preprocedure, four of the authors sought to reduce the severity of the thrombocytopenia. A platelet count of $<50 \times 10^9 \text{L}^{-1}$ generally prompted treatment consisting of corticosteroids, IV immune globulin, or platelet transfusion before block performance.

Only one source article made any mention of the platelet count at the time of epidural catheter removal. Frenk et al. described that, whenever possible, catheter removal was attempted only when the platelet count was in excess of $60\times 10^9 \text{L}^{-1}$. In spite of this, these authors reported that 5 of the 135 catheters studied were still removed (without consequence) when the platelet count was $<50 \times 10^9 \text{L}^{-1}$, though the reason for this apparent discrepancy was not explained in the article.

There were no reports of catastrophic or non-catastrophic hemorrhagic complications in the setting of ITP. Nonetheless, the data presented herein must be interpreted with caution.

The source articles included in this review are limited to case reports and case series with relatively few total subjects. In addition, the effects of negative reporting and publication bias cannot be discounted. Accordingly, it must be recognized that the absence of evidence does not imply evidence of absence. That is, just because the literature does not contain sufficient data regarding the frequency of hemorrhagic complications after neuraxial techniques in patients with bleeding diatheses does not mean that hemorrhagic complications do not occur often.

Vastly (and prohibitively) larger numbers of patients are required to determine the true incidence of epidural hematoma, as well as support or refute the safety of neuraxial techniques, in patients with ITP.

Moreover, the gross disproportions between surgical indication (e.g., obstetrics vs. orthopedics) and neuraxial technique type (e.g., lumbar epidural vs. spinal) undermine the validity of any general management recommendations that can be drawn from the present review for at important reasons. It has been shown that the prevalence of spinal hematoma after neuraxial techniques is considerably less in the obstetric population.
Relevant professional societies provide minimal, if any, evidence-based guidelines to assist anesthesiologists considering neuraxial techniques in patients with hemophilia, vWD, or ITP. Drawn from expert opinion, retrospective data and case reports, the widely cited consensus statements published by ASRA and the German Society of Anesthesiology and Intensive Care pertain exclusively to patients undergoing neuraxial techniques in the setting of hemeostasis altering medications.

Neither ASRA, European Society of Regional Anesthesia, the American Society of Anesthesiologists, the Canadian Anesthesiologists Society,† nor the American College of Obstetrics and Gynecology offers any guidelines for the practice of neuraxial techniques in patients with inherited coagulopathies or ITP. 34,35,59,127

Table 3 summarizes available recommendations from professional societies and government agencies regarding the provision of neuraxial techniques in the setting of hemophilia, vWD, or thrombocytopenia. 75,76 Importantly, each of these guidelines is based on expert opinion and/or case series with few patients.
### Guidelines for Neuraxial Techniques in Hemophilia, von Willebrand's Disease, and Thrombocytopenia

<table>
<thead>
<tr>
<th>Author/Reference</th>
<th>Society</th>
<th>Title</th>
<th>Bleeding diathesis</th>
<th>Level of evidence</th>
<th>Recommendations</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demers et al.²⁴</td>
<td>SOGC</td>
<td>Gynecological and obstetric management of women with inherited bleeding disorders</td>
<td>Hemophilia</td>
<td>V</td>
<td>Neuraxial techniques safe when coagulation factors normal</td>
<td>Normal' levels not defined No case series referenced</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vWD Type I</td>
<td>vWD recommendation based on single case report and case series reviewed herein²⁵,²⁶</td>
</tr>
<tr>
<td>Lee et al.⁶⁰</td>
<td>UKHDCO</td>
<td>The obstetric and gynecological management of women with inherited bleeding disorders</td>
<td>Hemophilia</td>
<td>V</td>
<td>Neuraxial techniques safe when coagulation factors &gt;0.5 IU mL⁻¹ Use milline technique with minimum local anesthetic concentration</td>
<td>No distinction made between vWD subtypes vWD recommendation based on single case report and single case series reviewed herein²⁷,²⁸</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vWD Type II</td>
<td>vWD recommendations based on 5 of 6 case series reviewed herein²⁹,³⁰,³¹,³²,³³,³⁴</td>
</tr>
<tr>
<td>Past et al.⁹¹</td>
<td>UKHDCO</td>
<td>Management of von Willebrand disease</td>
<td>vWD</td>
<td>V</td>
<td>Neuraxial techniques safe when coagulation factors &gt;0.5 IU mL⁻¹ Avoid neuraxial techniques in patients with vWD Types II and III</td>
<td>Rationale for avoidance in vWD Types II and III not explained No case series referenced</td>
</tr>
<tr>
<td>77</td>
<td>BCSH</td>
<td>Guidelines for the management of idiopathic thrombocytopenic purpura in adults, children, and in pregnancy</td>
<td>ITP</td>
<td>V</td>
<td>Platelet count &gt;60 × 10⁹ L⁻¹ recommended for neuraxial techniques</td>
<td>No case series referenced Conflicts with 2003 recommendations also published by BCSH in 2003 regarding platelet transfusions³⁵,³⁶</td>
</tr>
<tr>
<td>78</td>
<td>BCSH</td>
<td>Guidelines for the use of platelet transfusion</td>
<td>Thrombocytopenia</td>
<td>V</td>
<td>Platelet count &gt;60 × 10⁹ L⁻¹ recommended for neuraxial techniques and major surgical procedures</td>
<td>Based on single case series and 2 consensus statements³⁷,³⁸,³⁹,⁴⁰ Conflicts with 2003 recommendations also published by BCSH regarding management of ITP in pregnancy³⁵,³⁶</td>
</tr>
<tr>
<td>Schifer et al.⁹³</td>
<td>ASCO</td>
<td>Platelet transfusions for patients with cancer: clinical practice guidelines of ASCO</td>
<td>Thrombocytopenia</td>
<td>V</td>
<td>Platelet count &gt;40–50 × 10⁹ L⁻¹ recommended for neuraxial techniques and major surgical procedures</td>
<td>Based on 2 case series reviewed herein⁴¹,⁴²,⁴³</td>
</tr>
</tbody>
</table>

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It is noteworthy that lumbar puncture is frequently performed for diagnostic or therapeutic purposes in severely thrombocytopenic patients.

One literature search identified 5445 patients among eight published reports describing the use of neuraxial techniques in the setting of non immunologic thrombocytopenia (oncologic primary, chemotherapy or radiation induced)⁷⁷-⁸⁴
(Table 4) Data Summary of Lumbar Puncture or Caudal Injection in Nonimmunologic Thrombocytopenia

<table>
<thead>
<tr>
<th>Authors/Reference</th>
<th>Population/No.</th>
<th>No. of punctures</th>
<th>Prebleed platelet count (× 10⁹ L⁻¹)</th>
<th>Treatment</th>
<th>Cause/ type</th>
<th>Difficult/puncture</th>
<th>Outcome</th>
<th>Authors’ recommendations</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar puncture</td>
<td>Loe et al. 1993</td>
<td>ONC N = 4</td>
<td>4</td>
<td>Patient A—Pit = 46 post transfusion</td>
<td>N/A</td>
<td>A, D—transmanic hemostasis</td>
<td>None</td>
<td>All 4 cases resolved with conservative management and no neurologic compromise</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient B—Pit = 159</td>
<td>B—None</td>
<td>C—None</td>
<td>C, D—Subdural hemostasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient C—Pit = 8</td>
<td>D—None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient D—Pit = 250</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayerbe et al. 2010</td>
<td>ONC N = 1</td>
<td>1</td>
<td>Pit = 26</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Authors speculate that Pit = 25 too low for LP</td>
<td></td>
</tr>
<tr>
<td>Verreca et al. 2012</td>
<td>ONC N = 66</td>
<td>195</td>
<td>Pit = 101–140 (NT = 77)</td>
<td>Pit transfusion to ≥20</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Immediate surgical decompression</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pit = 50–100 (NT = 43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pit = 30–90 (NT = 75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Pit = 101–190 (NT = 3,234)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pit = 51–100 (NT = 800)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pit = 21–50 (NT = 742)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pit = 11–30 (NT = 170)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pit = 10 (NT = 5,700)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witz et al. 2007</td>
<td>ONC N = 1</td>
<td>1</td>
<td>Pit = 42</td>
<td>Pit transfusion, but no repeat Pit count</td>
<td>N/A</td>
<td>Subdural hemostasis with nonpermanent paraparesis</td>
<td>LP safe without transfusion if Pit ≥50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pit should be rechecked posttransfusion</td>
<td></td>
</tr>
<tr>
<td>Blalke et al. 2009</td>
<td>ONC N = 1</td>
<td>1</td>
<td>Pit = 10</td>
<td>None</td>
<td>1G</td>
<td>Subarachnoid hemostasis</td>
<td>None</td>
<td>Initial resuscitation for 48 h after symptom developed; temporary transfusion, target Pit ≥50</td>
<td>Surgical decompression 48 h after symptom developed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudal injection</td>
<td>Waldman et al. 196</td>
<td>N = 19</td>
<td>19</td>
<td>None</td>
<td>25G</td>
<td>25G</td>
<td>No complications</td>
<td>Caudal block safe with 25-G needle in severely thrombocytopenic patients</td>
<td>Authors indicate they have expanded use of technique to inject local anesthetic and epinephrine into epidural space</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(N = 19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic epidural</td>
<td>Wolff et al. 1996</td>
<td>ONC N = 1</td>
<td>1</td>
<td>Pit = 48</td>
<td>None</td>
<td>21-G needle</td>
<td>No asymptomatic epidural hemostasis</td>
<td>Pit count should be known before NT</td>
<td>Epidural hemostasis diagnosed on autopsy after unrelated death</td>
</tr>
</tbody>
</table>

Numeric values presented as ×10⁹ L⁻¹.

LP = lumbar puncture; N = number of patients; NT = number of LPs performed; ONC = oncologic patients thrombocytopenic from malignancy, chemotherapy, or radiation; Pit = Platelet.

3 Thirty-seven anticoagulated patients and 19 patients with nonimmunologic thrombocytopenia underwent 138 caudal blocks. Each patient with thrombocytopenia underwent more than one caudal block but authors did not indicate specific numbers.
These patients at higher risk for spinal hematoma because lumbar punctures are often performed by individuals with less experience, using larger gauge needles, in more severely thrombocytopenic patients, particularly in cases of leukemia, than neuraxial techniques performed by anesthesiologists.

Eight cases of spinal hematomas were reported in patients with platelet counts ranging from 8 to 250 \( \times 10^9 \text{ L}^{-1} \) and 2 needle insertions described as traumatic\textsuperscript{78, 80, 84} It seems plausible that, given identically low platelet counts, neuraxial techniques in the setting of leukemic thrombocytopenia may be more dangerous than in ITP in pregnancy, but this is wholly speculative.

Based on reports of only 326 neuraxial techniques, of which 325 were in the obstetric population, hemorrhagic complications after neuraxial techniques in patients with known ITP appear infrequent when the platelet count is more than 50 \( \times 10^9 \text{ L}^{-1} \) before block performance. The minimum “safe” platelet count for neuraxial blockade remain undefined in both the obstetric and general populations and evidence-based recommendations for neuraxial techniques in the setting of ITP cannot be offered.
OTHER ABNORMALITIES OF THE COAGULATION SYSTEM ASSOCIATED WITH HIV INFECTION

Currently available epidemiological evidence suggests that chronic HIV infection is associated with a two- to tenfold increased risk of venous thrombosis in comparison with a general population of the same age and the important risk factor for developing venous thrombosis is the severity of HIV infection.

Feffer et al.\(^{45}\) who found statistically significant correlation between the thrombotic potential in HIV-infected patients with degree of immune suppression (CD4 cell count) and presence of opportunistic infections and AIDS-related malignancies.

Table 5. Groups of Patients With AIDS Categorized in Relation to CD4 Cell Counts (Per Mm\(^3\)) and the Occurrence of Thrombotic Events

<table>
<thead>
<tr>
<th>CD4 count (Cell/mm(^3))</th>
<th>Total number of patients</th>
<th>No of patients with thromboembolic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>200-400</td>
<td>64</td>
<td>1</td>
</tr>
<tr>
<td>&gt;400</td>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

Aetiology

1. Increase in Procoagulant Factors

The increased risk of DVT in HIV-infected patients could be related to increased levels of procoagulant factors.

Endothelial cells could play an important role in the activation of the coagulation cascade during HIV infection\(^{86}\), the activation of endothelial cells, which normally behave as anticoagulant regulators, occurred during infections with viruses including HIV\(^{90}\), cytomegalovirus\(^{91}\) herpes virus and many others\(^{92}\).

HIV infection initiates intracellular signalling\(^{90,91}\) through the NFkB pathway, which results in both stimulation of an inflammatory response and in enhanced expression of tissue factor (TF) on the cell membrane. TF induces the extrinsic pathway of
coagulation by binding to factor VII and therefore is the major initiator of the coagulation cascade.

In HIV patients, increase numbers of micro particles, which originate from CD4+ lymphocytes, as a direct consequence of HIV infection and possibly as a reflection of CD4+ lymphocyte apoptosis, these micro particles are associated with activation of the coagulation cascade.

The pro coagulant properties of micro particles are believed to be caused by the clustering of coagulation factor complexes on the activated phospholipid surface serving as catalysts of coagulation reactions.

Even in the absence of high levels of micro particles, these elements may still contribute to enhanced coagulation activity, as seen in patients with multiple organ dysfunction syndrome and sepsis.93

2. Decrease in Anticoagulant Factors

The increased risk of DVT during HIV infection could also be related to the impaired functioning of several important anticoagulant proteins. In HIV-infected patients with thrombosis, lowered levels of antithrombin (AT) were reported94 which is the most important physiological inhibitor of activated coagulation factors (IIa, IXa, Xa, XIa and XIIa). Other anticoagulant proteins affected by HIV infection are protein C and protein S. Protein C is a potent anticoagulant which is activated after the binding of thrombin to thrombomodulin on the endothelial cell surface. Activated protein C (APC) inactivates the activated clotting factors V and VIII.94-96

Protein S has no known enzymatic activity but is an important co-factor for protein C, protein S deficiency have been reported in 65% of HIV-infected patients, reduced concentrations of protein S are associated with an increased risk of DVT.96 Heparin cofactor II (HC II anticoagulant protein) deficiency is significantly greater in HIV-positive individuals than in healthy subjects.97 Possible reasons for HC II deficiency could be decreased synthesis, enhanced proteolysis or consumption.

Antiphospholipid antibodies (APL) are proteins directed against different phosphor-containing lipids, the main constituents of cell membranes. The best known of these APL are anticardiolipin antibodies and lupus anticoagulants. Studies have shown APL to be present in 82 to 92% of patients with AIDS.98 APL are related to an increased occurrence of both venous and arterial thrombosis98, the increased risk for thrombosis can at least in part be explained by inhibition of activated protein C by anticardiolipin antibodies and their co-factor -glycoprotein I.
3. Specific HIV – Related Factors

In HIV-infected patients, significant increases of von Willebrand factor. Von Willebrand factor is a large endothelium-derived protein that mediates Platelet adhesion to damaged endothelium, which is the first step in haemostasis.

Furthermore, raised levels of both tissue type plasminogen activator (tPA) and its inhibitor plasminogen activator inhibitor I (PAI-I), were found in HIV patients, activation of both proteins indicates a general activation of the fibrinolytic system, probably as a reaction to the enhanced tendency to thrombosis (and secondary fibrinolysis).

Endothelial cell activation was also reflected in the detection of increased levels of soluble thrombomodulin (sTM) in HIV-infected patients. Soluble TM is an important co-factor for protein C, and probably the raised levels should also be considered a reaction to the various haemostatic changes.

In spite of the efficacy of HAART, HIV patients are still at increased general risk of infections. These concomitant infections are an additional risk factor for thrombosis. Cytomegalovirus infections were associated with pulmonary embolism and cerebral venous thrombosis. HIV infection can also be complicated by autoimmune hemolytic anemia. In this condition an increased risk of thromboembolic events, especially during infusion of red blood cells, was reported. Protease inhibitors may interfere with hepatic regulation of thrombotic proteins, therefore lead to prothrombotic estate in the HIV infected patient.

Fig 2 summarizing the hypercoagulable state in HIV–infected patient

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Page 22 of 40
DVT prophylaxis should be strongly considered among HIV patients with thrombotic risk factors (surgery, trauma, stasis, pregnancy, nephrotic syndrome, CMV infection, acute hospitalization), however HIV infected patient at higher risk of HIT than non infected patient.

Neuraxial anesthesia alone or combined with general anesthesia may reduce thromboembolic complications by several mechanisms, these include sympathectomy- induced increases in lower-extremity venous blood flow, systemic antiinflammatory effect of local anesthetic, decreased platelet reactivity, attenuated post operative increase in VIII, and von Willebrand factor, attenuated post operative decrease in antithrombin III, and alteration in stress hormone release. Intravenous lidocaine has been shown to prevent thrombosis, enhance fibrinolysis, and decrease platelet aggregation.89
NEUTROPENIA

Definition

Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1500/microL. The ANC is equal to the product of the white blood cell count (WBC) and the fraction of polymorphonuclear cells (PMNs) and band forms noted on the differential analysis:

\[
\text{ANC} = \text{WBC (cells/microL)} \times \text{percent (PMNs + bands)} \div 100
\]

Neutrophilic metamyelocytes and younger forms are not included in this calculation.

The risk of infection begins to increase at an ANC below 1000/microL (table 6)

Table 6  Neutropenia and Infection Risk

<table>
<thead>
<tr>
<th>Absolute neutrophil count/µL</th>
<th>Risk management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1500</td>
<td>none</td>
</tr>
<tr>
<td>1000-1500</td>
<td>No significant risk of infection, fever can be managed on an outpatient basis</td>
</tr>
<tr>
<td>500- 1000</td>
<td>Some risk of infection, fever can be occasionally managed on an outpatient basis</td>
</tr>
<tr>
<td>&lt;500</td>
<td>Significant risk of infection, fever should always be managed on a patient basis with IV antibiotic; few clinical signs of infection.</td>
</tr>
<tr>
<td>&lt;200</td>
<td>Very Significant risk of infection, fever should always be managed on a patient basis with IV antibiotic; few or no clinical signs of infection.</td>
</tr>
</tbody>
</table>
Aetiology

The aetiology of neutropenia is often multifactorial in HIV-infected patients, representing the combined effects of systemic infection, medications, and HIV itself (table 7).

- Many therapies used in the management of HIV, associated opportunistic infections, and malignancies can lead to clinically significant neutropenia. Zidovudine (AZT), trimethoprim-sulfamethoxazole, ganciclovir, hydroxyurea and combination chemotherapy for HIV-related malignancies are the most commonly implicated therapies.
- The use of highly active antiretroviral therapy (HAART) appears to be protective against the development of HIV-associated neutropenia, especially when using regimens not containing zidovudine.86
- Any opportunistic infection or malignancy that infiltrates the bone marrow may result in cytopenia. Mycobacterium valium complex (MAC), Mycobacterium tuberculosis, Histoplasma capsulatum, and other disseminated fungi are the most common infectious agents capable of infiltrating the bone marrow.
- Lymphomas, especially small, noncleaved cell, non-Hodgkin lymphoma, can produce pancytopenia through diffuse bone marrow involvement.
- Acute Epstein-Barr virus infection, dengue fever, viral hepatitis, parvovirus B19, rickettsial disease, salmonella infection, leishmaniasis, and brucellosis may all be associated with depressed neutrophil counts. Due to frequent co-infections in HIV, these should be considered based upon the history, such as travel.
- Cytomegalovirus infection can promote neutropenia through direct infection of marrow stromal elements and perhaps also myeloid cells.
- Antineutrophil antibodies have been detected using a granulocyte immunofluorescence test in almost one-third of patients with HIV. However, the presence of these antibodies does not correlate with the ANC. Thus, autoimmune destruction is not thought to play an important role in the pathogenesis of clinically significant neutropenia.86
- In addition to these secondary causes, HIV itself is a likely mediator of abnormal hematopoiesis in all cell lines. Many mechanisms have been proposed, including direct infection of early hematopoietic precursors, aberrations of local cytokine and growth factor signaling, and changes in the bone marrow stroma.
- In addition, circulating levels of granulocyte colony-stimulating factor (G-CSF) in HIV-positive patients are depressed when compared with healthy controls.86
### Impact of Neutropenia in Patients with HIV

Patients with HIV infection are more susceptible to serious, often life-threatening bacterial infections of many types, including bacteremia, pneumonia, meningitis, colitis and soft tissue infections, they are also at greater risk for invasive fungal infections with organisms such as Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum and Coccidioides immitis.

Invasive fungal infections are seen more frequently in patients with reduced circulating neutrophil counts; Candida and Aspergillus are common pathogens in this setting.

Many factors have been linked to these increased risks among HIV patients, including impaired cellular immunity, frequent usage of central venous catheters, altered mucosal integrity, and injection drug use (IDU).

The impact of neutropenia on overall mortality of patients with HIV infection remains unclear. Prospective data from the Women's Interagency HIV Study, a multicenter, longitudinal project assessing the medical course of over 2000 HIV-infected females and approximately 570 HIV-uninfected controls throughout the United States, failed to demonstrate any reduction in overall mortality among women with neutropenia defined as either an ANC <1000/microL or <2000/microL.102

### Administration of G-CSF or GM-CSF

Normal hematopoiesis is regulated by endogenous growth factors and cytokines. These glycoprotein hormones promote the proliferation of progenitor stem cells into increasingly differentiated cells and enhance the activity of mature blood cells.
Two endogenous glycoproteins — granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) — are major regulators of myelopoiesis, controlling the differentiation, proliferation, and functional activity of cells in the myeloid line.

GM-CSF stimulates various components of the myeloid line, especially neutrophils, monocytes and eosinophils. It also regulates multiple cellular functions, such as the inhibition of neutrophil migration and enhancement of the oxidative metabolism, chemotaxis, antibody-dependent cellular cytotoxicity and phagocytosis in mature neutrophils and macrophages.

Granulocyte colony-stimulating factor (G-CSF) more specifically exerts its control on the differentiation and functional capabilities of neutrophils. Both G-CSF and GM-CSF have an important role in the mobilization of stem cells from the bone marrow into the peripheral circulation.

Treatment with G-CSF
The benefits of rG-CSF have been established through multiple clinical trials in patients with HIV-associated neutropenia. The efficacy and safety of rG-CSF was evaluated in 200 patients enrolled in an open-label, multicenter trial. Neutropenia resolved in 98 percent of patients; this occurred after two days in more than one-half of these patients.¹⁰³

i. Effect on neutrophil function
Qualitative improvements in neutrophil function may also be observed. Polymorphonuclear cells exhibit augmented fungicidal activity and produce superoxide anions when incubated with Candida albicans and Cryptococcus neoformans.

ii. Effect on CD4 cells
There are conflicting data on the effect of G-CSF on the CD4 count. Both a transient increase and no change have been described. The percentage of CD4 + lymphocytes is generally unchanged.

Anesthetic implication
Concern has been expressed over the depression of cell-mediated immunity and alterations in immune function such as depression of natural killer cell, T-lymphocyte, monocyte and neutrophil activity after general anaesthesia. However, the changes seem to be transient and do not lead to increased of postoperative infection. It has been suggested that immune changes do not occur after regional techniques but there is insufficient evidence to recommend regional over general anesthesia in HIV infection on immunological grounds alone.
ANEMIA

Incidence and Significance
Anemia is the most common hematologic abnormality associated with HIV infection, affecting 60 to 80% of patients in late stage disease. While anemia may manifest as a mere laboratory abnormality in some individuals, others may experience typical symptoms (eg, fatigue, dyspnea, reduced exercise tolerance, diminished functional capacity) directly related to a reduction in hemoglobin concentration.

The incidence of developing anemia increases with disease progression, affecting 3% of all patients with asymptomatic HIV infection, 12% of asymptomatic patients with CD4 cell counts <200/microL, and 37% of patients with an AIDS-related illness.87

Risk factors
Risk factors for the development of anemia (Hgb<12g/dl) are
- Mean corpuscular volume (MCV) <80 fL — OR 4.2 (95% CI 2.8-6.2)
- CD4 count <200/microL — OR 2.0 (95% CI 1.6-2.4)
- HIV-1 viral load ≥50,000/mL — OR 1.7 (95% CI 1.4-2.1)
- Use of AZT in past six months — OR 1.7 (95% CI 1.4-2.0)

The presence of anemia is associated with increased morbidity and mortality in HIV infected patient.87-90 Despite the advent of HAART, HIV-related anemia is still common, and independently associated with decreased survival.

Aetiology
In most cases, the cause of anemia in HIV-infected patients is multifactorial, (infection, malignancy, malnutrition, and polypharmacy). The finding of a low hematocrit or hemoglobin concentration warrants careful evaluation for treatable underlying illnesses, including a complete blood count with red cell indices and reticulocyte count, serum bilirubin and vitamin B12, red cell folate levels, iron studies, peripheral blood smear and, in cases of refractory or unexplained anemia, serum erythropoietin and bone marrow sampling.87

1. Infections
Opportunistic processes must be carefully excluded during the evaluation of anemia. Although many infections may be associated with cytopenias in HIV-infected patients, several are characteristically linked to abnormalities of red blood cell production.
a. **Mycobacteria**
Mycobacteria and fungi are capable of broad dissemination throughout the bone marrow, eventually replacing the normal architecture and inhibiting the maturation of progenitor cells. Mycobacterium avium complex (MAC), M. tuberculosis, and Histoplasma capsulatum are the most common offenders. In rarer cases, other agents such as Pneumocystis carinii, Cryptococcus neoformans, and Penicillium marneffei have caused pancytopenia through bone marrow infiltration.87

b. **Viral infections**
Viral infections may be associated with suppression of normal bone marrow function. Mild-to-moderate anemia is a common finding in patients with acute cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection in addition to HIV.

2. **Malignancy and lymphoproliferative disorders**
Infiltration of the bone marrow by malignant cells is a potential cause of anemia and other cytopenias. The small noncleaved cell type of non-Hodgkin lymphoma is the most common offender (Burkitt-like), followed by other aggressive and highly aggressive malignant lymphomas and, rarely, Kaposi's sarcoma.

3. **Nutritional deficiencies**
Nutritional deficiencies are common in patients with advanced immunosuppression, stemming from the combined impact of anorexia, medication-associated gastrointestinal disturbances, wasting and malabsorption. The aetiology of vitamin B12 deficiency in these patients has been linked to malabsorption in the distal ileum, achlorhydria with a secondary reduction in intrinsic factor production, and an alteration in cobalamin transport proteins.

Folate deficiency can occur in HIV-infected patients and may result from reductions in both dietary intake and intestinal absorption. Folate deficiency should be considered in patients at high risk for reduced dietary intake and those with an elevated mean corpuscular volume or megaloblastic changes on blood smear.104

Abnormal iron metabolism; Iron studies are typically consistent with the anemia of inflammation (anemia of chronic disease), characterized by reduced concentrations of serum iron and total iron binding capacity and a normal or increased concentration of serum ferritin. In some cases, however, there is evidence of iron deficiency anemia, typically related to gastrointestinal blood loss.104
4. **Hemolysis**

Hemolysis may play a role in HIV-associated anemia. A variety of mechanisms may be involved, including antibody-mediated hemolysis, drug-induced disease in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and microangiopathic hemolytic anemia.

Antibody-mediated; the presence of antibodies directed against red cell antigens is more common than overt hemolysis.\(^{105}\) Drug-induced — a number of drugs can be associated with hemolysis in patients with HIV infection. Dapsone and primaquine therapy may cause mild reductions in hemoglobin values. Severe, life-threatening hemolysis occurs in HIV-infected patients with G6PD deficiency who are exposed to these or other medications with oxidant potential. Ribavirin therapy is commonly associated with the development of hemolytic anemia. Thus, patients co-infected with HIV and hepatitis C who receive combination therapy with alfa-interferon and ribavirin should be carefully monitored for the development of clinically significant anemia.

Microangiopathic hemolysis is a hallmark of disseminated intravascular coagulation (DIC) secondary to bacterial sepsis and is also seen in thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS).

5. **Bone marrow suppression**

Multiple therapies used in the management of HIV infection and its related conditions can suppress erythropoiesis.

a. **Zidovudine (AZT)**

   Bone marrow suppression is the most common toxicity observed in patients treated with zidovudine (AZT).

b. **Other agents**

   Bone marrow suppression can be induced by many other drugs used for the prophylaxis or therapy of opportunistic processes, including ganciclovir, valganciclovir, hydroxyurea, Amphotericin B, and TMP-SMX.

6. **Possible role of HIV**

HIV itself appears to be a major contributor to abnormalities in hematopoiesis. Retroviral infection has been clearly demonstrated in CD4+ lymphocytes, macrophages, monocytes, and follicular dendritic cells.

Some of these differences may be explained by observations that the ability of the HIV-1 subtype C to infect hematopoietic progenitor cells is greater than that of HIV-1 subtype B. This hematotropism was found to be associated with higher rates of anemia in southern Africa, where infection with HIV-1 subtype C is more common.\(^{87}\)
Role of Bone Marrow Examination
Bone marrow aspiration and biopsy is often performed during the evaluation of anemia and other cytopenias in patients with HIV infection.

A broad spectrum of biopsy findings can be seen, but no histologic abnormality can be considered pathognomonic.\textsuperscript{87}

- Normocellular marrows are the most common, occurring in over 70 percent of patients in one series. Hypercellularity and, less often, hypocellularity were seen in the remaining patients.
- Increased plasma cells, histiocytes and marrow reticular cells have been noted in many series.
- Frank megaloblastic changes may be noted in patients receiving AZT or those with severe B12 or folic acid deficiencies.

Bone marrow aspirates and biopsies may reveal the etiology of anemia by demonstrating infiltrative malignancies, infiltrative infections caused by mycobacteria or fungi, or the characteristic giant pronormoblasts encountered in parvovirus B19 disease. The one advantage of marrow sampling is the rapidity with which a histologic diagnosis may be made. Thus, in patients with a rapidly changing clinical picture, the speed of processing justifies marrow sampling.

Treatment
Treatment of anemia in HIV-infected patients should begin with treatment of the HIV infection as well as correction of all of the reversible causes of anemia present in that particular patient. (See 'Aetiology' above.)

1. HAART
Reduces both the incidence and degree of anemia in all groups of HIV-infected patients (ie, men, women, injection drug users), however some patient with a significant risk of developing anemia despite treatment with HAART \textsuperscript{87}, and these risk factor are;
- mean corpuscular volume (MCV) <80 fL
- CD4 count <200/microL
- HIV-1 viral load >50,000/mL.
- use of AZT in the past six months.
- CD4 count <100/microL
2. Correcting reversible causes of anemia
In addition to primary treatment of the underlying HIV infection, therapy of the anemia should also focus on correcting potentially reversible causes:
- Infectious aetiologies warrant aggressive treatment.
- Uncommon hematologic complications, such as warm autoimmune hemolytic anemia and thrombotic thrombocytopenic purpura appear to respond to standard treatments for these diseases.
- Intravenous immune globulin is the therapy of choice for patients with pure red cell aplasia and documented parvovirus B19 infection.
- Treatment with therapeutic doses of vitamin B12, folate, and/or iron is indicated when one or more of these deficiencies are detected.
- When clinically feasible, attempts at dose reduction or discontinuation of implicated medications should be considered. When discontinuation of medications is not possible, or when secondary causes are not identified, alternative strategies for augmenting red blood cell reserves are indicated (eg, transfusion, use of erythropoietic stimulating agents).

3. Blood transfusion
Transfusion remains the mainstay of therapy for acute, life-endangering blood loss or severely symptomatic anemia of any cause. While the administration of packed red blood cells offers rapid correction of anemia and reversal of symptoms, there are several inherent risks, such as transfusion reactions, transmissible infection (eg, viral hepatitis, HTLV-I, CMV), and development of alloantibodies and, when repeated transfusion is required, iron overload and its associated complications.

a. CMV status
To minimize the risk of CMV transmission to CMV-seronegative recipients, most experts advocate the use of CMV-seronegative blood. When CMV-seronegative blood is not available, blood products should be administered through a leukocyte filtering system. However, since the majority of HIV-infected patients have evidence of past CMV infection, this approach is rarely necessary.106

b. Transfusion-associated graft versus host disease
Because HIV-infected patients are immunocompromised, the possibility of developing transfusion-associated graft-versus-host disease (ta-GVHD) has been raised for those receiving unmodified red blood cells.87
c. **Viral activation**

It is the potential risk of enhanced viral activity or impaired immunologic function after the transfusion of blood products.

It has been suggested that the infusion of blood products may directly activate HIV replication. Compatible with this hypothesis are the following observations:

- In a prospective comparison of the impact of factor VIII infusions on HIV progression in hemophiliacs, more rapid decrements in CD4 counts were noted in patients who received intermediate-purity versus high-purity factor infusions (in this case, factor VIII purified with monoclonal antibodies).
- Another study compared 360 patients who received blood transfusions within the first three months after AIDS diagnosis to untransfused patients with comparable levels of anemia. After controlling for the severity of illness, there was a trend toward reduced survival in the patients who had received transfusions.

4. **Recombinant Human Erythropoietin**

Recombinant human erythropoietin has been approved by the United States FDA for the treatment of anemia (eg, elevate/maintain red blood cell level and decrease the need for transfusions) associated with HIV (zidovudine) therapy although no studies have evaluated the effect of EPO on overall survival of these patients.

Therapy with rEPO should be reserved for patients with symptomatic anemia in whom serum erythropoietin concentrations are <500 IU/L. Iron reserves should be monitored throughout therapy and replenished as necessary. An initial rEPO dose of 100 U/kg subcutaneously three times weekly is usually recommended. In most cases, increases in hematocrit are evident after two weeks. Dose escalation by 50 U/kg should be considered if no response has been noted after four to eight weeks of therapy; further increases are recommended every four to eight weeks until reaching the targeted hematocrit or the maximal rEPO dose (300 U/kg).

Recombinant erythropoietin is generally well tolerated. The most common side effects encountered are nausea, headache, hypertension, seizure, and rash or local reactions at the injection site.
CONCLUSION

• The incidence and severity of thrombocytopenia in HIV infected patient is associated with the stage of disease, severe thrombocytopenia (platelet count $50 \times 10^9/L$) is associated with clinical AIDS, CD4 lymphocyte count of $< 200/µL$, age $> 45$ years, intravenous drug use and, lymphoma and/or anemia.

• The minimum “safe” platelet count for neuraxial blockade remains undefined in both the obstetric and general populations.

• The incidence of anemia in the HIV-infected patient is considerable, even in the HAART era. The presence of anemia is associated with increased morbidity and mortality in patients with HIV infection.

• Blood should only be transfused where unavoidable as blood transfusion is associated with increased mortality.

• If transfusion of packed red blood cells is required: the red cell products should be leukoreduced and irradiated.

• Strict aseptic technique should be exercised as HIV infected patients are immunocompromised and are susceptible to bacterial infections.

• DVT prophylaxis should be strongly considered among HIV patients with thrombotic risk factors, and thrombotic events in young patients with HIV risk factors may suggest the possibility of AIDS.
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