

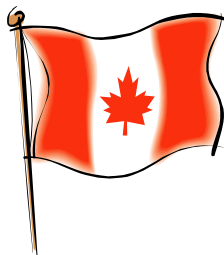
A Nurse's Guide

For Assessment and Management of Patients Diagnosed with Paget's Disease of Bone

A Publication of

**The Paget Foundation
for Paget's Disease of Bone and
Related Disorders**

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Introduction

After osteoporosis, Paget's disease is the second most common metabolic bone disease, but it often goes unrecognized and untreated until its course has advanced. Nurses, radiologists and other health care professionals who work in hospital emergency rooms, nursing homes and family clinics should be aware of Paget's disease and its symptoms and complications, in order to identify patients as early as possible and utilize the effective treatments that are available to manage this disease.

In one typical diagnostic scenario, an elderly person suffers a broken bone in an accident and a radiologist recognizes Paget's lesions on the x-rays. Other patients, assuming that they have arthritis, treat Paget-related bone pain with increasing amounts of over-the-counter medications. They do not know or learn that the source of the pain is Paget's disease until they receive a proper diagnosis, sometimes years after the pain began.

Nurses, who are on the front-line of health care, need to know what to look for and what questions to ask in order to diagnose Paget's disease early in the disease's progression. The earlier a diagnosis is made, the more effective the treatment, and the less devastating the impact on the individual patient.

What is Paget's Disease of Bone?

First described by the eminent British surgeon Sir James Paget in 1877, Paget's disease of bone is a disorder of bone remodeling in which there is excessive bone resorption followed by excessive bone formation that results in bone that is architecturally unsound. The disease occurs in both males and females, affecting 1.5% to 8% of the population over 50 years of age in many countries. It is much less common in people of Asian, Indian and Scandinavian ancestry.

Paget's disease may be found in multiple family members due to mutations in several genes. There is also evidence of measles virus in bone lesions in Paget's disease, but the relevance of this is still under investigation.

Pathology of Paget's Disease

The initial abnormality in Paget's disease is a dramatic increase in the rate of bone resorption in one or more areas of the skeleton. Pagetic osteoclasts are abnormal – approximately five times larger than normal containing an average number of 20 nuclei per cell compared with three to four nuclei in normal adult osteoclasts. However, the osteoblasts, though numerous, are not abnormal. Because bone resorption triggers bone formation, the rate of bone resorption is matched by a rapid rate of bone formation over time. The new bone is structurally disorganized, however, resulting in an overall decrease in bone strength and an increase in susceptibility to bowing and fractures. In addition, a high level of vascularity and an excess of fibrous connective tissue in the marrow mark the abnormal bone.

Clinical Presentation

Paget's disease may cause the enlargement and deformity of a single bone or multiple bones. As a result, bone pain, arthritis, noticeable skeletal deformities and fractures can occur. While any bone can be affected, the most common sites are the femur, tibia, pelvis, vertebrae and skull. Long bones in the leg tend to bow, and the skin over the Pagetic lesion is frequently warm due to the increased blood flow to the site. The skull can become enlarged and lead to headaches or hearing loss when the disease affects the temporal bone. In advanced cases, the spine may develop curvature. In the spine, the increased bone volume may compress the spinal cord or nerve roots, causing severe pain and impaired neurological functioning. Hip pain is a common complaint when the pelvis or thigh bone is involved. Clinical signs and symptoms will vary from one patient to the next, depending on the number and location of affected skeletal sites, as well as on the rapidity of the abnormal bone turnover. Long-term observation of Paget's disease patients indicates that the disease does not spread from one bone to another.

The most devastating complication of Paget's disease is a transformation of the bone that becomes cancerous. Fortunately, osteosarcoma or other types of sarcoma occur in less than 1% of patients with Paget's disease, but this is a significantly higher rate than in non-affected individuals. In patients with Paget's disease, osteosarcoma is often fatal.

Guidelines for Assessment

It is likely that many patients have the disorder for a long period before any diagnosis is made, especially because Paget's disease is often asymptomatic and the diagnosis may be an incidental finding. Paget's disease can be discovered in patients through radiology, radionuclide bone scanning, biochemical testing of bone resorption parameters, or biochemical testing of bone formation parameters. At least one measurement of bone metabolic activity and x-rays of affected bones are the minimum recommended level of evaluation to track and monitor the progression of treatment in a patient with Paget's disease.

Biochemical Tests

Elevated levels of the enzyme serum alkaline phosphatase (SAP) detected in routine serum chemistry profiles can be the first indication that an individual has Paget's disease and not arthritis or another disorder. Alkaline phosphatase, an enzyme produced by bone cells and a marker for bone formation, is over-produced by Pagetic bones. A mild over-production might indicate a healing fracture, but a SAP level two or more times higher than normal strongly suggests Paget's disease, provided there is no evidence of liver disease or renal failure.

Biochemical tests that serve as markers of bone resorption and disease activity may support the diagnosis of Paget's disease. These tests include urinary hydroxyproline, pyridinoline/deoxypyridinoline, N-telopeptide and C-telopeptide.

Radiographic Testing

Bones affected by Paget's disease have a characteristic appearance on x-rays. These characteristic changes include the presence of osteolytic lesions and enlarged bones with a chaotic sclerotic appearance. A decrease in joint space is an indication of degenerative arthritis, a common disorder in patients with Paget's disease.

Radionuclide Bone Scan

A radionuclide bone scan is the most sensitive means of detecting Paget's disease in the skeleton. A radiolabeled bisphosphonate is injected intravenously and circulates through the blood stream. This substance then localizes in Pagetic areas of bone where there is increased blood flow and high levels of bone formation. This test is used primarily to

establish the full extent of Paget's activity. It is not generally used to monitor the effects of treatment.

Medical History

The diagnosis of Paget's disease for patients in clinical settings begins with obtaining a careful medical history. This history includes documentation of family members who have been diagnosed with the disease. Specific symptoms related to Paget's disease should be sought including pain (onset, location, severity), deformity and increased warmth over an extremity. General history taking includes documentation of current and previous medical conditions, fractures, surgeries, medications, height (maximum and current) and weight. Patients who come for a second opinion regarding a previous diagnosis of Paget's disease should be queried regarding the following:

- Date of diagnosis
- How the diagnosis was made
- Skeletal site/s affected
- Date of diagnostic test (bone scan, x-ray, lab test)
- Serum alkaline phosphatase (SAP) level
- Current/previous Paget's medications
- Symptoms
- Previous fractures
- Physical function limitations
 - a. Activities of daily living
 - b. Mobility
 - c. Balance
 - d. Hearing.

A complete medical history, physical examination and interpretation of laboratory test results contribute to making an accurate diagnosis and identifying the appropriate management strategy.

Objectives for Management of Paget's Disease

The three major objectives for the management of patients with Paget's disease are:

1. Minimize symptoms;
2. Improve the patient's physical function; and
3. Help slow the disease process, limit disability and prevent complications.

The nurse plays a major role in helping the patient accomplish each of these objectives by providing the patient and family members with education and professional support and by encouraging the patient's adherence to therapy.

Indications for Treatment

Treatment for Paget's disease is based on antiresorptive therapy. There are four general indications for treatment of Paget's disease:

1. Symptoms due to metabolically active Paget's disease warrant treatment, including bone pain related to a pagetic site or fatigue fracture, headache resulting from an affected skull, back pain from affected pagetic vertebrae or other neurological syndromes associated with Pagetic changes.
2. Many Paget's disease specialists believe that treatment is indicated as an attempt to decrease local progression and reduce the risk of future complications – even in asymptomatic patients whose sites of disease and degree of metabolic activity place them at risk of progression and complications. This group of patients includes individuals who may be at risk for: A) bowing deformities in their long bones; B) hearing loss because of skull enlargement; C) neurological complications due to Pagetic changes in their vertebrae; D) secondary arthritis as a complication of Paget's disease located next to major joints.
3. Treatment is warranted in a patient planning to undergo elective surgery on a pagetic site, such as hip replacement, in an attempt to minimize the operative blood loss due to hypervascularity present in active Pagetic bone.
4. Treatment is indicated in the management of hypercalcemia, a rare occurrence when a patient with multiple bones affected by Paget's disease and a highly elevated serum alkaline phosphatase level undergoes prolonged immobilization.

Although there is no direct evidence that aggressive treatment of Paget's disease is associated with prevention of progression or reduction in risk of future complications, investigators have looked to indirect evidence to suggest this possibility. This indirect evidence includes the assumptions that:

1. Failure to treat Paget's disease is associated with the further extension of the osteolytic lesions in a bone and the progression of bone deformities;
2. Successful treatment of Paget's disease is associated with restoration of normal patterns of new bone deposition; and
3. Improvement of facial and skull deformities may be observed after successful treatment (shown in one study).

Therefore, Paget's disease specialists conclude that it is good clinical practice to treat both symptomatic patients, whose symptoms may improve after a reduction in abnormal bone turnover, and asymptomatic patients who have active Paget's disease in areas of the skeleton that might be expected to produce future complications of clinical significance.

Adherence to Therapy

Be aware of the emotional impact of the words "Paget's disease".

Increasing concern about skeletal health, risk of complications and safety of drug therapy are major concerns that can produce stress and anxiety in individuals who have been diagnosed with Paget's disease. Counseling patients can promote implementation of new behaviors to optimize bone health, reduce further consequences and enhance quality of life. The targets of such counseling are: A) behaviors related to adherence to medical therapy, B) injury prevention and C) physical therapy when indicated. Continuous collaboration between nurses and patients can help improve adherence. Factors that may negatively influence adherence include the patient's unfulfilled expectations and/or inadequate explanation of the disease to the patient. The nurse's approach to each patient should be specific, individualized, consistent and nonjudgmental. It is important for the nurse to understand the following patient issues to help the patient make appropriate changes in health behaviors:

1. Individual health beliefs;
2. Motivation to change and level of commitment; and

3. Presence or absence of denial of risk or severity of disease.

Counseling techniques to promote and maintain new health behaviors include:

1. Provide specific individual information regarding diagnosis risks, cost and benefits of medical therapy, including side effects, duration of treatment and cost;
2. Set mutual goals;
3. Provide patient with flowsheet to document diagnostic test dates, laboratory results, medication (doses, start& stop dates, side effects).
4. Provide feedback regarding response to therapy;
5. Encourage long-term follow-up; and
6. Dispel fears and misperceptions.

Therapy Options

Four main methods of treatment exist for a patient with Paget's disease:

1. Non-pharmacological therapy (focusing mainly on physical therapy as a means of improving muscle strength to help control some types of pain);
2. Pharmacological therapy using either bisphosphonates or calcitonin;
3. Pain management using analgesics; and
4. Surgery.

Pharmacological Treatment

Bisphosphonates

Bisphosphonates suppress or reduce bone resorption by osteoclasts. They do this both directly by hindering the recruitment and function of osteoclasts and perhaps indirectly by stimulating osteoblasts to produce an inhibitor of osteoclast formation. There is now a reasonable understanding of how bisphosphonates work, and the differences between the various types of bisphosphonates are better understood.

Five bisphosphonates are currently available in Canada for the treatment of Paget's disease. These include three oral bisphosphonates (alendronate, risedronate, and etidronate) and two intravenous (IV) bisphosphonates (zoledronic acid 5 mg and pamidronate). As a rule, oral bisphosphonate should be taken on an empty stomach and

patients should not lie down for at least 30 minutes after taking the bisphosphonate tablet. For IV bisphosphonates, there are no restrictions on when and what you can eat, and there are no restrictions on normal activities such as lying down, standing, sitting, taking a walk or exercising. Specific instructions for taking each drug are included in the table that follows.

An adequate dietary calcium intake (1000-1500 mg daily) and Vitamin D intake (800 units daily) are recommended during bisphosphonate use, except if there is a history of kidney stones that contain calcium. For all bisphosphonates, SAP levels should be tested on a regular basis (i.e., 3 months after the treatment period).

Both alendronate and risedronate have also been shown to reduce SAP into the normal range in patients with moderate-to-severe Paget's disease. In addition, a single infusion of zoledronic acid 5 mg has been shown to produce more rapid, more complete and more sustained responses in Paget's disease than daily treatment with risedronate (30 mg daily for 60 days).

Investigators have recognized that secondary resistance to individual bisphosphonates (i.e., etidronate and pamidronate) can occur. Therefore, it may be necessary for a patient to switch from one bisphosphonate to another in long-term treatment. Due to the generally poor absorption of the oral bisphosphonates, it is vital that patients take oral bisphosphonates in the prescribed manner to avoid incomplete absorption of the drugs. With intravenous (IV) bisphosphonates such as zoledronic acid 5mg, absorption is not an issue, and zoledronic acid 5 mg offers Paget's patients strong bone protection in a single dose.

Calcitonin

Subcutaneous injection of salmon calcitonin was the first widely utilized therapy for Paget's disease. Salmon calcitonin has been shown to reduce elevated indices of bone turnover by 50%, decrease symptoms of bone pain, reduce warmth over affected bones, improve some neurological complications and promote healing of lytic lesions. However, today the use of calcitonin is limited mostly to patients who do not tolerate bisphosphonates. In the case of secondary resistance to salmon calcitonin, a switch to bisphosphonate therapy is necessary.

The drug therapies most widely recommended by Paget's disease medical specialists are the three more potent bisphosphonates: zoledronic acid 5mg (Aclasta[®]), risedronate (Actonel[®]), and alendronate (Fosamax[®]).

Pain Management: Analgesics

Pain directly attributable to Paget's disease is generally relieved through antiresorptive (i.e., bisphosphonate) treatment as described above. Some pain may be the result of muscle spasm associated with either bone deformity or arthritic or neurological complications. In this case, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS) or the new cox-2 inhibitors may be helpful for the management of nonskeletal pain in addition to the main pagetic therapy chosen.

Surgery

Different orthopedic interventions that may be necessary in patients with Paget's disease include:

1. Fixing a complete fracture through Pagetic bone;
2. Realigning the knee through tibial osteotomy to decrease mechanical pain, particularly if pharmacotherapy is unsuccessful in managing severe pain symptoms; and/or
3. Replacing the hip and/or knee through total joint arthroplasty for patients unresponsive to anti-osteoclast treatment and therapy for the osteoarthritis.

When repairing a pagetic fracture, total immobilization of that site should be avoided if possible. In all cases of surgical intervention, pre-surgery treatment with a potent bisphosphonate is very important. Since hypervascularity is a feature of active Paget's disease, this may lead to serious bleeding during an operation. Pre-treatment with a bisphosphonate will reduce the hypervascularity and reduce the risk of greater-than-normal operative blood loss.

INFORMATION ON ADMINISTRATION AND DOSAGE OF DRUGS APPROVED IN CANADA FOR THE TREATMENT OF PAGET'S DISEASE†

The table below outlines information about all drug therapies and recommended doses approved by Health Canada for Paget's disease. The approval year for each therapy is for the Paget's disease indication. Please note that experienced physicians may sometimes prescribe different doses. None of these drugs should be used by people with severe kidney disease.

NOTE: Although some of these drugs are also approved for use in osteoporosis, the doses and treatment duration may be different depending on whether Paget's disease or osteoporosis is being treated.

I. Bisphosphonates	Administration and Dosage
<p>Zoledronic Acid 5 mg Trade name: Aclasta[®] Manufacturer: Novartis</p> <p>Approved by Health Canada in 2005.</p>	<ul style="list-style-type: none"> • A single dose of 5 mg Aclasta[®] administered by intravenous (IV) infusion in <u>no less than</u> 15 minutes. • Patients should drink 2 glasses of water (i.e., 2 cups or 500 mL) before and after the Aclasta[®] infusion. • No restrictions on when and what to eat or drink. • No restrictions on normal activities such as lying down, standing, sitting, talking a walk or exercising. • It is recommended that Paget's patients have their renal function assessed before treatment with Aclasta[®] (i.e., as part of their annual examination). • Aclasta[®] is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).
<p>Risedronate Sodium[‡] Trade Name: Actonel[®] Manufacturer: Procter & Gamble</p> <p>Approved by Health Canada in 1999.</p>	<ul style="list-style-type: none"> • 30 mg tablet taken by mouth, once daily for 2 months. • Actonel[®] should be taken on an empty stomach and may be taken: <ul style="list-style-type: none"> - At least 30 minutes before the first food or drink (other than plain water) of the day; or - At least 2 hours from any food or drink other than plain water (i.e., nothing to eat or drink for at least 2 hours

	<p>before and 2 hours after dosing).</p> <ul style="list-style-type: none"> - Not less than 30 minutes before bedtime. • Actonel[®] should be shallowed with sufficient plain water (≥ 120 mL). • Patients should not lie down for at least 30 minutes after taking Actonel[®] (patient may sit). • Actonel[®] is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).
<p>Alendronate Sodium[‡] Trade Name: Fosamax[®] Manufacturer: Merck Approved by Health Canada in 1995.</p>	<ul style="list-style-type: none"> • 40 mg tablet taken by mouth, once daily for 6 months. • Fosamax[®] must be taken at least 30 minutes before the first food, beverage, or medication of the day with plain water only. <ul style="list-style-type: none"> - Tablet should only be taken upon arising for the day. - Tablet should be swallowed with a full glass of water (i.e., 200-250 mL). - Tablet should not be taken at bedtime or before arising for the day. • Patients should not lie down for at least 30 minutes after taking Fosamax[®] and until after their first food of the day. • No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). • Fosamax[®] is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min).
<p>Pamidronate Disodium Trade Name: Aredia[®] Manufacturer: Novartis Approved by Health Canada in 1994.</p>	<ul style="list-style-type: none"> • Intravenous (IV) infusion • The recommended total dose of Aredia[®] for a treatment course is 180 to 210 mg. This may be administered either as: <ul style="list-style-type: none"> - 30 mg once a week for 6 weeks (total dose 180 mg); or - infusions administered every 2 weeks. Initial dose (week 1) = 30 mg; Subsequent doses (weeks 3, 5 & 7)

	<p>= 60 mg. Total dose: 210 mg.</p> <ul style="list-style-type: none"> • A course of Aredia® may be readministered at intervals as needed. • Serum creatinine (a measure of kidney function) should be periodically evaluated especially in patients who receive frequent pamidronate infusions over a prolonged period of time, and those with pre-existing renal disease or a predisposition to renal impairment.
<p>Etidronate Disodium Trade Name: Didronel® Manufacturer: Procter & Gamble Approved by Health Canada 1977.</p>	<ul style="list-style-type: none"> • 200 to 400 mg tablet taken by mouth, once daily for 6 months • Didronel® should be taken on an empty stomach at least 2 hours before or after meals with a full glass of water. • A course of Didronel® should not exceed 6 months. • Repeat courses can be given after rest periods of at least 3 months duration. • Since absorbed Didronel® is excreted through the kidneys, periodic renal function assessment should be carried out in patients whose renal function may be deteriorating. While there is no experience to specifically guide treatment in patients with impaired renal function, in such cases renal function should be monitored carefully.

† Please note that some of these medications may be available in non-branded (i.e., generic) formulations. Please consult your physician for the treatment option that is best for you.

‡ IMPORTANT NOTE: Fosamax®, Actonel® and Didronel® should be used with caution by patients who have disorders affecting the esophagus or the stomach.

II. Calcitonin	Administration and Dosage
<p>Calcitonin Salmon Trade name: Caltine® Manufacturer: Ferring</p>	<ul style="list-style-type: none"> • Injection (sub-cutaneous or intra muscular) • 100 IU (international units) injected per day until a decrease towards normal SAP levels is observed; usually within first few months

Approved by Health Canada in 1992.	
Calcitonin Salmon Trade name: Calcimar® Manufacturer: Aventis Approved by Health Canada in 1978.	<ul style="list-style-type: none"> • Injection (sub-cutaneous or intra muscular) • 100 IU (international units) injected per day until a decrease towards normal SAP levels is observed; usually within first few months

The cost of these drugs varies depending on which province a patient lives and his or her insurance coverage.

Conclusion

The development of specific inhibitors of osteoclast-mediated resorption, particularly the potent bisphosphonates, has brought about major changes to the treatment of Paget’s disease in the past 25 years. Although the long term effects of disease suppression is unknown, the capacity to restore the bone remodeling process to normal gives reason to believe that reduction in long term complications and their related morbidity is now possible.

The Paget Foundation for Paget's Disease of Bone and Related Disorders is a voluntary health agency that provides information and programs for consumers and health professionals on several bone disorders including: Paget's disease of bone, primary hyperparathyroidism, fibrous dysplasia, osteopetrosis (not the more common disease osteoporosis), and the complications of certain cancers on the skeleton.

Foundation programs and services include:
Patient Education and Assistance, Professional Education, Public Education,
Research & Advocacy

A copy of the Foundation's annual report is available by writing to the Foundation office or the Office of the Attorney General, Charities Bureau, 120 Broadway, New York, NY 10271.



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