

Heterotopic Ossification (HO)

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I. Definition, Assessment, Diagnosis

A. Definition.

1. Heterotopic ossification (HO) is a process by which ectopic bone is formed in the soft tissue surrounding peripheral joints⁵. Osteoprogenitor stem cells lying dormant in the surrounding soft tissues with a stimulus (such as hip surgery, spinal cord injury (SCI), and stroke) differentiate into osteoblasts and cell lines involved in bone formation. These cells then calcify and form well-organized bone over a several month period.
 - a. Previous studies¹³ suggest that ectopic bone formation require three conditions: osteogenic precursors, an inducing agent, and an environment permissive to osteogenesis. There is likely a connection between stimulation of mesenchymal cells followed by osteoprogenitor maturation and osteoblast activation.
 - b. Histopathologic studies show normal endochondral osteogenesis at heterotopic sites. They noted six distinct histological stages: (1) perivascular lymphocytic infiltration, (2) lymphocytic migration into soft tissue, (3) reactive fibroproliferation, (4) neovascularity, (5) cartilage formation, and (6) endochondral bone formation.²²
 - c. It is thought genetic predisposition, such as HLA B27, combined with presence of osteoblast stimulating factors and prostaglandins contribute to ectopic formation.¹³ Studies show there are increased stimulating factors and osteoblastic activity in animals with SCI.¹⁴
 - d. Though the relationship between central nervous system and bone is not completely understood, neurotransmitters likely have an effect on bone metabolism.
 - e. Phagocytic macrophages, rather than osteoclasts, recruited in inflammatory muscle are also thought to be responsible for triggering neurogenic HO development.⁹ Targeting phagocytic macrophage recruitment is a promising therapeutic approach to prevent neurogenic heterotopic ossification (NHO).
 - f. These results supported the previous finding that naïve muscle progenitor cells are capable of mineralizing secondary to inappropriate CNS signaling that reprograms progenitor cells to osteogenesis instead of muscle repair.
 - i. Risk factors. HO can be either acquired or neurogenic.
 - ii. Acquired HO (AHO), which is more common, can occur after any type of musculoskeletal trauma or injury, such as total hip arthroplasty, fractures, burns or hip dislocations.
 - iii. NHO is most common in patients with SCI, traumatic brain injury (TBI), and less common in stroke.

- iv. Reported to occur in 16-53% of patients after SCI. Most common locations are hip, knee, shoulder, and elbow.
- v. Incidence after TBI ranges from 11-28%⁵ commonly affected by immobility, spasticity, and fractures. Dysautonomia may also be a risk factor.
- vi. Numerous sources have investigated potential factors contributing to development of HO. A case-control study on patients with traumatic spinal cord injury who developed HO were identified through a database and assessed for signs/symptoms of HO at different time points in time following discharge. Findings showed that patients with complete spinal cord lesions had greatest risk for HO development. The presence of spasticity, thoracic trauma, pneumonia, and nicotine use increased risk for development. There was no correlation between age, sex, race, or length of hospital stay.^{6,7}

B. Assessment

I. Signs and Symptoms

- a. Warmth, swelling, and erythema over a joint.
- b. Fever. This may be the only sign, and can mimic infection.^{6,11}
- c. Gradual decrease in joint mobility.

II. Rule out other causes of symptoms

- a. Vascular System
 - i. Deep Vein Thrombosis
- b. Infectious
 - i. Cellulitis
 - ii. Osteomyelitis
- c. Oncologic
 - i. Osteosarcoma
 - ii. Osteochondroma

C. Diagnosis

I. Imaging

- a. Triple phase bone scan is the gold standard for diagnosis of HO as it shows findings earlier than radiographs, but can be negative in the first couple of days in the acute phase of diagnosis.
- b. The early stage of HO maturation consists of immature bone not yet detectable by radiographs.¹⁷
- c. MRI can be confidently used for the diagnosis of exclusively mature HO, since the signal associated with early HO lesions is heterogeneous.²³
- d. 3D CT scanning¹ offers a more accurate approach for guiding surgical excision of HO. Patients found to have significant HO of the hip following SCI or TBI were scanned and classified based on location; anterior, medial, lateral, posterior, and mixed. Use of 3D imaging was more accurate than classifying NHO based on radiologic findings. Other

benefits include proper assessment of neurovascular structures, easier excision in cases of incomplete HO, and decreased risk of iatrogenic injury.

- e. Ultrasound may be more specific in differentiating HO from other traumatic, inflammatory, or degenerative diseases of skeleton than bone scan. It has been shown to detect earlier than traditional radiographic studies and like 3D CT, can be used to visualize HO prior to surgical excision.¹² It can also reasonably be used to follow maturation of HO as documented in prior studies.¹⁹ It is used more extensively in Europe, and has good sensitivity but specificity data is lacking.²⁵

II. Laboratory Data

- a. Alkaline phosphatase (ALP) levels can rise around first 2 weeks of injury in patients who develop HO and may return to baseline values at approximately 10-12 weeks.²
- b. Although ALP is nonspecific for osteogenic activity, this inexpensive test may be useful adjunct in diagnosis of early HO.
- c. Elevated prostaglandin 24-hour urinary excretion in patients with suspicious symptoms may be helpful when determining need for bone scan.¹⁵
- d. Although nonspecific, Creatinine Kinase (CK) is typically higher in HO SCI patients and often suggests more involvement of surrounding muscle.¹⁶
- e. C-Reactive Protein correlates better with inflammatory activity of HO after SCI than does ESR. ESR was found to remain elevated even when clinical signs and symptoms weren't present.⁸

II. Management and Treatment Recommendations

A. Management and Treatment Recommendations.

- I. Recognition of signs, symptoms, and risk factors.
- II. Physical examination of joint and interpretation of available imaging and lab values.
- III. Obtain appropriate imaging study. Triple phase bone scan should be first line.
 - a. If initial bone scan is negative but clinical findings are highly suggestive of HO, NSAIDs such as Indomethacin can be used to down regulate prostaglandins thought responsible for cell differentiation into new bone formation.^{4, 24}
 - b. Prophylactic use of three weeks of indomethacin vs three weeks of placebo in SCI patients showed a significantly lower incidence of HO in treatment group vs placebo, and those in treatment group developed HO significantly later than placebo.⁴ NSAID prophylaxis appears to help prevent HO development during the acute phase after SCI.²⁴
 - c. Use of the Bisphosphonate, Etidronate in groups with positive bone scan and negative radiographic findings vs. positive for both imaging modalities. Showed that clinically significant HO can be prevented if

treatment started before HO visible on radiographs. Ultimately, no significant difference was found between the two groups in development of HO.^{2,3}

- d. Alendronate (ALN) use and HO incidence was assessed in a retrospective study in an acute rehab setting. There was on evidence of HO prevention but abnormal serum ALP was found more frequently in patients with HO development and without oral ALN intake. This evidence could suggest that ALN may play a role in preventing HO, especially in patients with acute SCI with increasing levels of serum ALP.²⁰
- e. Radiotherapy can be used as primary or secondary prevention, either in conjunction with surgical excision or prophylactically in patients with severe injuries in whom HO development is high.^{12,17} It has been shown to be safe and effective for treatment of HO, but long term followup is lacking for late radiation side effects.²⁶
- f. Botulinum toxin A injected to cause transient muscle paralysis in a mice model of HO mitigated the formation of HO in this model. This may suggest another treatment strategy to manage HO in the acute phase of development.²¹
- g. Surgical excision of the HO is done to improve mobility and function. It is typically only performed: if HO interferes with self-care or sitting in wheelchair; or it contributes to development of pressure ulcers, or causes compression of nerves and blood vessels.¹⁷ Previous studies suggested waiting for maturation of heterotopic bone prior to excision. However, recent studies suggested there is no relationship between surgical intervention relative to onset and risk of recurrence. Therefore, NHO excision should occur when it begins to be troublesome, as soon as comorbid factors are under control, and the HO is sufficiently constituted for excision.¹⁰

III. Prevention and Education

A. Potential complications

- I. If HO not addressed and managed in a timely manner multiple problems can develop: loss of joint mobility, decreased range of motion for ADLs and a loss of mobility can result.
 - a. Peripheral nerve entrapment
 - b. Decreased ROM progressing to ankylosis
 - c. If HO overlies bony prominence, this directly predisposes to pressure ulcer/skin breakdown.^{12,17}

B. Prevention

- I. Prophylaxis.
 - a. Evidence shows that early treatment with NSAIDs in acute SCI reduces the incidence of HO.²⁴
 - b. Warfarin has been associated with decreased HO and may be beneficial if administered after SCI. More studies are likely needed to validate this conclusion.
 - c. Initiation of bisphosphonates such as Etidronate is most effective if initiated

early. However, long term use in patients with concomitant bone injuries may impair fracture healing.

- d. Radiotherapy is thought to halt progression of HO by irradiating mesenchymal pluripotential cells. Studies show when used as secondary prevention, it may improve joint range of motion and help prevent recurrence.¹⁸

C. Education

- I. After diagnosis is confirmed, completion of prescribed medication with a bisphosphonate and NSAID and is recommended for resolution of HO.
- II. Close follow-up with physician is key in management of this condition and prevention of recurrence.

This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.

Guideline Developers

Guideline developed by Amanda Price, MD, in collaboration with the TRIUMPH team led by Thomas S. Kiser, MD, and Rani H Lindberg, MD.

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