Heterotopic ossification (HO) is the pathological formation of bone in soft tissues. Despite being first described in very early medical literature almost 1000 years ago, this condition still poses significant problems in modern times, most notably amongst military combat casualties (Fig. 1). The relationship between military injuries and HO was first discussed in the medical literature of the American civil war. Damanski describes how, subsequent to this early description, multiple accounts of HO appeared in the medical literature describing civilian and military occurrences of this condition under various names such as myositis ossificans, ostiasis neurotica para-articularis, paraossalis, and ossifying myopathy. Writing about experience gained in the field today:

"Excessive terminal bone production in... stumps was the rule. The most common form was an irregular mushrooming with a tendency to spurs on the inner aspect of the femur. Occasionally sharp exostoses were seen. These often were sharp enough and long enough to cause sufficient pain to warrant their removal." 

The recent conflicts in Iraq and Afghanistan have provided further examples of how HO can present a significant challenge as a consequence of combat injury. The burden of HO has been so great that Alfieri et al. have described it as an "epidemic" and argue that it is the single biggest barrier to functional recovery for combat-injured patients.

**Genetic Forms of HO**

HO may be caused by genetic or acquired factors. The genetic forms of HO are not the focus of this review but have relevance due to historical attempts to treat them and the insights that they provide into pathological bone formation. The pathological mechanism that causes the genetic form of HO known as fibro-osseous ossification (FOP) (Fig. 2) has been studied extensively and is well characterized: A heterozygous single nucleotide substitution of arginine to histidine (R206H) in the ACVR1 gene. This gene encodes for the activin A type I receptor (ACVR1) gene. This gene encodes for the protein activin-like kinase 2 (ALK2), which is a receptor for bone morphogenetic proteins (BMPs). ALK2 has greater sensitivity to the ligand, BMP-2, leading to increased phosphorylation and nuclear localization of SMAD proteins, and increased Id1 promoter activity. Increased ALK2 activity subsequently leads to increased chondrogenic and osteogenic differentiation and the formation of bone in ectopic sites through enchondral ossification.

In contrast to FOP, progressive osseous heteroplasia (POH) occurs through intramembranous ossification and its genetic basis is less well characterized but is thought to involve heterozygous mutations in the GNAS1 gene. The mutation inactivates the GNAS1 gene, which encodes for the alpha subunit of Gsα, and it is thought that this leads to dysregulation of cell lineage switching, resulting in excessive osteogenic differentiation of mesenchymal stem cells (MSCs).
Post Traumatic HO

HO may develop after almost any significant injury but is particularly common after blast injury, high-energy transfer gunshot wounds, central nervous system injury, burns, hip replacement surgery, acetabular fractures, and elbow injuries. It is not clear whether a single common cellular and biochemical mechanism is responsible for the development of HO secondary to each of these causative events.

Epidemiology of Post-Traumatic HO

Radiological evidence of HO was found in 64.6% of a cohort of combat injured patients. A similar figure of 62.9% is reported in a series of combat-injured patients who had undergone amputations. In the blast injury subset of these cases, where amputation was performed through the zone of injury, the rate of radiographically moderate or severe HO rose to 79.6%. It is worth noting that in the Afghanistan conflict, from 2003 to 2014, British service personnel suffered 416 combat amputations from 265 patients (giving the mean limbs lost per patient as 1.6).19

A retrospective observational study of civilian amputations demonstrated that 22.8% of patients developed symptomatic HO. HO is also common amongst patients with traumatic brain injury (radiological evidence in 37% of patients), spinal cord injury (5–60%), hip arthroplasty (5%), distal humerus fractures (8.6%), and burns (0.15%).25

Leading researchers in the field have commented that the incidence of HO has been much higher in the cohort of injured combatants from the Iraq and Afghanistan conflicts compared to historical data. Potter et al. propose that the reasons for this increase in HO include a high incidence of blast injury (due to increased use of explosive weaponry) and increased survival amongst seriously injured combatants (due to improvements in body armor, medical care, forward surgical treatment, and rapid evacuation).26

Thus the combination of exposure to blast, extremity amputation, and improved survival (Fig. 3) is thought to have generated an extent and severity of HO not seen before. Historically, patients with these injuries would not have survived long enough to develop symptomatic HO after combat trauma.

Clinical Impact of Post-Traumatic HO

Patients with HO experience a wide range of problems due to the mechanical effects of hard tissue in extraskeletal sites. These include pain, loss of joint range of motion, joint ankylosis, skin ulceration, overlying skin graft failure, muscle entrapment, neurovascular entrapment, and prosthetic limb fitting difficulties. Evriviades et al. described the clinical impact of HO on patients eloquently as follows: ‘‘The development of HO can occur in the soft tissues very early and is sometimes found even before primary healing occurs. However, in the majority, it occurs after a number of months. The patient will typically have had an [improvised explosive device] injury and sustained bilateral...''
traumatic above-knee amputations (often with other significant injuries), and will have initially done well with limb fitting and mobilization. They may develop increasing pain in their stumps and can often feel a hard lump or spike within the stump. In severe cases, the bone has actually eroded through the soft tissues. This may prevent them from mobilizing and poses a significant challenge to the prosthetics team.

Given the high prevalence of HO after civilian and combat-related limb amputations, it is worth noting the problems that these patients have with limb fitting. In the civilian setting, 50% of patients with HO require prosthetic modifications such as selective padding, hard socket reshaping, or new socket fabrication. In the military setting, there are no published data on the proportion of patients requiring prosthetic modification due to HO. However, Pascale and Forsberg et al. clearly describe how HO causes a significant clinical burden for this cohort including activity modification and socket or liner adjustment.

Financial Cost of Post-Traumatic HO

There are no published data on the direct financial costs of HO. However, some indication may be gained from a paper by Masini et al. who estimate that the direct cost of disability benefits for US service personnel with extremity injury sustained during the campaigns in Iraq and Afghanistan between October 2001 and 2005 to be $1.2 billion. Given that more than 10 years of conflict continued after the publication of that report, the true figure is likely to be vastly more than this estimation. If 64% of combat extremity injuries develop HO (see above), the proportion of this cost estimate that relates to HO prevention, treatment, and rehabilitation is likely to be substantial.

Another analysis, looking at the long term financial cost associated with UK military amputees has identified that approximately £288 million will be required over the next 40 years. Again, this analysis does not specifically estimate the contribution that HO will make to this total figure but it illustrates that the magnitude of the financial cost in addition to the clinical and personal burden to the individuals.

Current Prophylaxis

There are currently no methods of primary prophylaxis that are entirely appropriate for the military population who are likely to be catabolic, at risk of gastric ulceration and renal injury, have open wounds and fractures, and are often in austere environments.

Non-Steroidal Anti Inflammatory Drugs (NSAIDs)

NSAIDs are used widely in civilian practice to cover a variety of situations where patients are at high risk of developing HO. An example is revision total hip replacement surgery where the patient has demonstrable HO secondary to the initial operation. However, there is evidence that, in addition to their normal side effect profile, NSAIDs increase the risk of non-union in the setting of HO prophylaxis after acetabular fixation. Impairment of fracture healing would be a particularly problematic side-effect in major trauma patients as they are highly likely to have sustained at least one fracture as part of their pattern of injuries. Further, these patients are likely to have high risk of kidney injury, which is a major contraindication to NSAID use.

Radiotherapy

Radiotherapy is also used in the elective civilian setting and has been shown to be effective but there is lack of consensus on timing and dose. Radiotherapy and NSAIDs may be given in combination for high-risk patients. There is a paucity of data to guide the use of radiotherapy in the traumatic injury cohort. Even if there was good evidence, the logistical challenges to delivering radiotherapy in austere environments are considerable. Further, there are multiple adverse effects of radiotherapy such as impaired growth.
wound and bone healing, which mean that it would be contraindicated in military patients who often have co-synchronous fractures and extremely challenging soft tissue wounds. For example, Hamid et al. have demonstrated that a single-fraction dose of radiotherapy (700 cGy) given to elbow trauma patients as prophylaxis against HO was associated with a nearly 10-fold increase in the rate of non-union.40

**Bisphosphonates**

Bisphosphonates are a class of drugs whose primary use is to prevent and treat osteoporosis. They have also been prescribed as prophylaxis against HO. However, their use remains controversial after a Cochrane review41 and other studies42 failed to find conclusive evidence of efficacy. There have been no studies looking at their role after major trauma.

**Passive Movement Therapy**

Another Cochrane review43 investigating the use of passive movement physiotherapy in a heterogeneous group of patients (including traumatic brain injury and spinal cord injury patients at risk of HO) concluded that there is insufficient evidence show whether or not this therapy is effective.

**Experimental Prophylaxis**

One strategy that has shown immense promise is retinoic acid receptor gamma (RARγ) agonist to inhibit chondrogenesis.44 Without a cartilage scaffold, the endochondral processes that form HO are blocked and no mineral can be deposited. It is worth noting that, in the rodent model, there was a transient prolongation of fracture healing associated with RARγ agonism. Despite this concern, the treatment was so effective that the RARγ agonist palovarotene has been taken forward into clinical trials (NCT02279095) as a treatment for FOP.45

Another novel strategy has been demonstrated in a burn-tenotomy rodent HO model46 whereby hydrolysis of adenosine triphosphate (ATP) at the burn site led to reduced HO formation at a distant site. In addition to revealing a potential therapeutic strategy, this “remote ATP hydrolysis” method provides a further mechanistic insight into the role of phosphorylated SMAD proteins in the development of HO.

In another rodent tenotomy model (without burn injury), treatment with the antibiotic echinomycin inhibited HO formation.47 The proposed mechanism is that echinomycin inhibits hypoxia-induced factor 1-α (HIF-1-α), a signalling molecule thought to be crucial to the process of chondrogenic differentiation of mesenchymal stem cells in HO.

Further evidence of the potential of antibiotic drugs to prevent HO comes from recent work in a rodent high-energy extremity trauma model.48 Early topical vancomycin reduced the burden of HO in this model, independent of whether or not the wound was infected. As with the work using echinomycin (above), this suggests that the relevant action of vancomycin is not mediated through its antibiotic activity.

It is important to note that all of the experimental and extant prophylaxes work by attempting to inhibit the cellular and/or biochemical pathways that are thought to cause HO. There are no published data on experimental or clinical treatments that have been designed to directly inhibit or disperse the mineral component of heterotopic ossification.

**Current Treatment**

**Non-Operative Management**

Rest, analgesia, nerve blocks, and nerve ablations form the mainstay of non-surgical treatments.11 However, once HO has formed and matured, it has not been shown to regress or remodel significantly, so patients who remain symptomatic after optimization of non-surgical management options will often require surgery.

**Operative Management**

In a civilian amputation study, 25% of patients were treated with NSAIDS, 8% with bisphosphonates, and 11% underwent surgery to resect the ectopic bone.20 In a series of military patients, 19% required surgical excision, with a mean interval between injury and excision of 8.2 months.18 Excision had a significant effect on the analgesic requirements of the patients: 63% were able to cease opioid analgesia completely. There is debate about the exact timing of surgery. If HO is excised too early then it may recur but waiting too long may delay the patient’s rehabilitation and return to function. A systematic review of studies of HO excision after brain injury did not find evidence to support the view that early surgery predisposes to recurrence.49 With appropriate timing of surgery and secondary prophylaxis with NSAIDS and/or radiotherapy, recurrence of HO rarely requires further surgery. For example, in a large series of patients who had undergone primary HO excision secondary to acquired brain or spinal cord injury, only 5.8% required further surgery due to recurrence.22 Recent practice for secondary prophylaxis amongst UK military surgeons excising HO has been to prescribe a 4-week course of oral indomethacin (with concomitant gastric protection such as a proton pump inhibitor) starting in the immediate post-operative period.31 Potter et al. have reported that high quality evidence to guide the choice of secondary prophylaxis is lacking.18

Despite the success of operative interventions in controlling HO, it must be stressed that these operations are technically extremely challenging and come with significant risks of adverse events such as bleeding and damage to remaining soft tissues.31 Standard practice at the UK Defence Medical Rehabilitation Centre, Headley Court, is that amputee patients are non-weight bearing for 6 weeks after surgery to their stumps (personal communication). Given that these patients can have multiple operations for soft tissue reconstruction, any additional requirement for surgery due to HO excision can add to their
already significant period of non-weight bearing and this can have lasting effects on their rehabilitation potential.

**Pathophysiology**

**Signalling and Cellular Factors**

There is significant controversy in the literature about the fundamental cellular and molecular mechanisms involved in acquired HO formation. Candidate cell populations of mesodermal, ectodermal, and endodermal origin have all been proposed. One of the key problems is that while there are many cell types that may be influenced to produce mineralization in vitro or in vivo, this does not mean that they are responsible for HO in patients. Davies et al. reviewed the evidence for and against all of these candidates and concluded that it is most likely that HO results from complex signalling networks involving multiple cell types (Fig. 4). However, consensus is building to favor the direct role of multipotent cells of mesenchymal origin.

One example of how intercellular signalling is important in the formation of HO comes from the work of Olmsted-Davis et al. They used a mouse bone morphogenic protein (BMP-2) model to demonstrate that hypoxic adipocytes were required for the differentiation of stem cells to chondrocytes, which is a key early step in the formation of ectopic bone. In addition to illustrating the role of multiple cell populations in the formation of HO, this work demonstrates that local physicochemical environment may play a role. Tissue hypoxia may not only stimulate intercellular signalling but will also lead to reduced pH through cellular anaerobic respiration. Low pH will, in turn, have an effect on the chemical phases that are stable in that environment and may even be exploited for the purposes of preventing and treating HO.

Recent work has provided evidence that different cell types may even generate phenotypically distinct HO subtypes. In an Acvr1R206H knock in mouse model that phenotypically resembles the genetic form of HO (FOP), Mx1+ cells produced injury-dependent intramuscular HO whereas Scx+ cells lead to injury-independent ossification of ligaments and tendons.

**The Role of Inflammation**

There is significant support in the clinical and basic science literature for the central role of an exaggerated inflammatory response in the pathogenesis of HO. It is well recognized that patients who have suffered major trauma demonstrate a multiphasic inflammatory dysregulation after injury with both acute and chronic components. This seems to fit with the observed clinical experience of HO in a number of interesting ways. It might explain why HO develops after weeks to months and then progresses for months to years, after which time it stabilizes and becomes quiescent. It may also explain why the timing of excision surgery is important if recurrence is to be avoided. This inflammation hypothesis is

---

**Figure 4.** (A) The potential direct and indirect contribution of well-characterized cells such as myoblasts and satellite/progenitor cells and the potential involvement of under-characterized resident cells such as muscle interstitium cells and side population MSC-like cells. (B) The paracrine roles of endothelial cells, as well as the potential direct contribution of these cells through endothelial-mesenchymal transition (EMT). Reproduced with permission from Davies et al.
supported by the most comprehensive work to date characterizing the effect of timing of surgery on HO recurrence, which recommended that at least 180 days should elapse between injury and attempted complete excision.\textsuperscript{65}

**Ossification Mechanism in HO**

It has been shown that there is upregulation in key osteogenic and chondrogenic gene transcripts (BMP2, BMP3, ALPL, COL2A1, COL10A1, COL11A1, COMP, CSF2, CSF3, MMP8, MMP9, SMAD1, and VEGFA) in the soft tissues of high-energy combat wounds.\textsuperscript{66} The upregulation of these gene transcripts suggests an endochondral (as opposed to an intramembranous) model of development of acquired HO, something that has been confirmed separately in an animal model.\textsuperscript{67,68}

**Early Detection**

Currently, HO is diagnosed using imaging techniques. However, significant benefits may be gained by earlier identification and better risk stratification of those patients who will go on to develop HO. Reliable risk stratification and prediction allows clinicians to target prophylactic therapies at the right patients thus reducing the risk of harmful side effects in those who would never have developed HO anyway. The increasing knowledge of cellular and biochemical pathophysiology of this condition has allowed the development of several techniques that set out to achieve this goal. For example, one group has shown that serum levels of interleukin (IL) 3 and 12p70 and wound effluent levels of IL-3 and 13 at the time of first debridement predicted those would go on to develop HO.\textsuperscript{59,60} However, it must be noted that these studies have not predicted those would go on to develop HO.\textsuperscript{59,60} It has been shown that there is upregulation in key osteogenesis-related genes between patients that developed HO and those who did not. This study may, however, be confounded by the finding that the HO group had a significantly higher injury burden, more bacterial colonization, bigger wounds, and more amputations than the non-HO group.

**DISCUSSION**

Post-Traumatic HO is a fascinating and debilitating condition (or perhaps group of conditions) that has been known about for a long time. For many years it has been regarded as a rare complication of central nervous system injury or an inconvenient adverse effect of major surgery and so a handful of prophylactic approaches were discovered and developed to attempt to prevent it in those settings. However, since 2003, with the beginning of the conflicts in Iraq and Afghanistan and the subsequent on-going unrest in the region, our experience of this condition has changed completely. This is due to the alignment of a unique set of circumstances: Increased incidence of blast injuries, increased incidence of combat-related amputations, and vast improvement in survival of even the most seriously injured patients. The result of this is that we have seen a significant increase in both the incidence and severity of this disease. The few prophylaxes that had been developed to prevent HO in the civilian setting have been shown to be either ineffective or inappropriate for the complex and often multiply injured military casualties, who are thus left at high risk of developing HO. Furthermore, even if we had an effective prevention strategy, early reliable detection and risk stratification is not yet available to guide administration of such and intervention. Despite their severe injuries, these patients have been shown to have a high potential for good functional outcome with appropriate rehabilitation.\textsuperscript{69,70} However, it has been claimed that the single biggest barrier to achieving this potential is HO. This is because not only does it prevent patients from using the highly advanced prosthetics that are made available to them but also because the surgery required to excise HO introduces multiple long delays into their rehabilitation, which have a cumulative deleterious effect on their final functional outcome.

**CONCLUSIONS**

Post-traumatic HO represents a significant threat to the rehabilitation potential of patients after major injury. There is an unmet need for improvements in early detection, risk stratification, and effective prophylaxis in this cohort. Promising progress has been made in all of these areas but no new solutions have made their way to clinical practice yet. The time to drive progress in this area is now, so that when the next major conflict emerges, we are prepared to counter this age-old problem with brand new approaches.

**REFERENCES**

1. Spink MS, Lewis GL. Albucasis: on surgery and instruments: a definitive edition of the Arabic text with English translation and commentary: Wellcome Institute of the History of Medicine 1973.
2. Patin G. Lettres choisies de feu. Guy Patin Coldene 1692:28.
3. Otis G, Huntington D. 1883. Wounds and complications. The medical and surgical history of the Civil War 2:880.
4. Damanski M. 1961. Heterotopic ossification in paraplegia. Bone Joint J 43:286–299.
5. Dejerine A, Ceillier A. 1918. Para-osteo-arthropathies des paraplegiques par lesion medullaire; etude clinique et radiographique. Ann Med 5:497.
6. Dejerine M, Ceillier A, Dejerine Y. 1919. Para-osteo-arthropathies des paraplegiques par lesion medullaire. Etude anatomique et histologique. Revista de Neurología 26:399–407.
7. Riedel B. 1883. Demonstration line durch ach Hagiges Umhergehen total destruirten kniegelenkes von einem patienten mit stichverletzung des ruckans. Verh Dtsch Gesellschaft Chirurg 12:93.

8. Geldmacher M. 1925. Beitrag zu den parartikulären Verknöcherungen nach Querschnittsläsion des Rückenmarks. Langenbecks Arch Surg 191:180–196.

9. Israel A. 1920. Über Myositis ossificans neurotica nach Schußverletzung des Rückenmarks. Fortschr Röntgenstr 27:365.

10. Brackett EG. 1921. Care of the amputated in the United States. Washington: US Government Printing Office. p 713–748.

11. Alferri KA, Forsberg JA, Potter BK. 2012. Blast injuries and heterotopic ossification. Bone Joint J 1:192–197.

12. Culbert AL, Chakkalakal SA, Convente MR, et al. 2013. The changing pattern of amputations. J R Army Med Corps 159:300–303.

13. Shore EM, Xu M, Feldman GJ, et al. 2006. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet 38:525–527.

14. Fukuda T, Kohda M, Kanomata K, et al. 2009. Constitutively activated ALK2 and increased SMAD1/5 cooperatively induce bone morphogenetic protein signaling in fibrodysplasia ossificans progressiva. J Biol Chem 284:7149–7156.

15. Kaplan FS, Shore EM. 2000. Progressive osseous heteroplasia. J Bone Miner Res 15:2848–2855.

16. Pascale BA, Potter BK. 2014. Residual limb complications and management strategies. Curr Phys Med Rehabil Rep 241–249.

17. Shore EM, Xu M, Feldman GJ, et al. 2006. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet 38:525–527.

18. Potter BK, Burns TC, Lacap AP, et al. 2007. Heterotopic ossification following traumatic and combat-related amputations. Prevalence, risk factors, and preliminary results of excision. J Bone Joint Surg 89:476–486.

19. Edwards MD, Phillips LCRD, Bosanquet N, et al. 2015. What is the magnitude and long-term economic cost of care of the British military Afghanistan amputee cohort? Clin Orthop Rel Res 473:2758–2765.

20. Matsumoto ME, Khan M, Jayabalan P, et al. 2014. Heterotopic ossification in civilians with lower limb amputations. Arch Phys Med Rehabil 95:1710–1713.

21. Dizdar D, Tiftik T, Kara M, et al. 2013. Risk factors for developing heterotopic ossification in patients with traumatic brain injury. Brain Inj 27:807–811.

22. Genêt F, Jourdan C, Schnitzler A, et al. 2011. Troublesome heterotopic ossification after central nervous system damage: a survey of 570 surgeries. PLoS ONE 6:e16632.

23. Berstock J, Blom A, Beswick A. 2015. A systematic review and meta-analysis of complications following the posterior and lateral surgical approaches to total hip arthroplasty. Ann R Coll Surg Engl 97:11–16.

24. Nauth A, McKee MD, Ristevski B, et al. 2011. Distal humeral fractures in adults. J Bone Joint Surg 93:686–700.

25. Chen H-C, Yang J-Y, Chuang S-S, et al. 2009. Heterotopic ossification in burns: our experience and literature reviews. Burns 35:857–862.

26. Potter BK, Burns TC, Lacap AP, et al. 2006. Heterotopic ossification in the residual limbs of traumatic and combat-related amputees. J Am Acad Orthop Surg 14: S191–S197.

27. Brown KV, Clasper JC. 2013. The changing pattern of amputations. J R Army Med Corps 159:300–303.

28. Brown KV, Dharm-Datta S, Potter BK, et al. 2010. Comparison of development of heterotopic ossification in injured US and UK Armed Services personnel with combat-related amputations: preliminary findings and hypotheses regarding causality. J Trauma Acute Care Surg 69:S116–S122.

29. Penn-Barwell JG, Roberts SA, Midwinter MJ, et al. 2015. Improved survival in UK combat casualties from Iraq and Afghanistan: 2003–2012. J Trauma Acute Care Surg 78:1014–1020.

30. Potter BK, Forsberg JA, Davis TA, et al. 2010. Heterotopic ossification following combat-related trauma. J Bone Joint Surg 92:74–89.

31. Evriviades D, Jeffery S, Cubison T, et al. 2011. Shaping the military wound: issues surrounding the reconstruction of injured servicemen at the Royal Centre for Defence Medicine. Philos Trans R Soc Lond B Biol Sci 366:219–230.

32. Forsberg JA, Potter BK. Heterotopic ossification in wartime wounds: DTIC Document, 2010.

33. Pascale BA, Potter BK. 2014. Residual limb complications and management strategies. Curr Phys Med Rehabil Rep 241–249.

34. Masini BD, Waterman SM, Wenke JC, et al. 2009. Resource utilization and disability outcome assessment of combat casualties from Operation Iraqi Freedom and Operation Enduring Freedom. J Orthop Trauma 23:261–266.

35. Beckmann JT, Wylie JD, Kapron AL, et al. 2014. The effect of NSAID prophylaxis and operative variables on heterotopic ossification after hip arthroscopy. Am J Sports Med 42:1359–1363.

36. Leib T, Hughes M, Anglen J. 2003. Heterotopic ossification prophylaxis with indomethacin increases the risk of long bone nonunion. J Bone Joint Surg 85:700–705.

37. de Abreu KLS, Silva Junior GB, Barreto AGC, et al. 2010. Acute kidney injury after trauma: prevalence, clinical characteristics and RIFLE classification. Indian J Crit Care Med 14:121–128.

38. Popovic M, Agarwal A, Zhang L, et al. 2014. Radiotherapy for the prophylaxis of heterotopic ossification: a systematic review and meta-analysis of published data. Radiother Oncol 113:10–17.

39. Pakos EE, Pitouli EJ, Tsokos PG, et al. 2006. Prevention of heterotopic ossification in high-risk patients with total hip arthroplasty: the experience of a combined therapeutic protocol. Int Orthop 30:79–83.

40. Hamid N, Ashraf N, Bosse MJ, et al. 2010. Radiation therapy for heterotopic ossification prophylaxis acutely after elbow trauma: a prospective randomized study. JBJS 92:2032–2038.

41. Haran M, Bhuta T, Lee B. 2004. Pharmacological interventions for treating acute heterotopic ossification. Cochrane Database Syst Rev 4:D003321.

42. Shafer DM, Bay C, Caruso DM, et al. 2008. The use of eidoronate disodium in the prevention of heterotopic ossification in burn patients. Burns 34:355–360.

43. Prabhu RKR, Swaminathan N, Harvey LA. 2013. Passive movements for the treatment and prevention of contractions. Cochrane Database Syst Rev 12:CD009331.

44. Shimono K, Tung W-E, Macolino C, et al. 2011. Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor-[gamma] agonists. Nat Med 17:454–460.

45. Johnson RW, Sims NA. 2014. Embedded in bone, but looking beyond: osteocalcin, epigenetics and ectopic bone formation (ASBMR 2014). IBMS BoneKEy 11.

46. Petersson JR, De La Rosa S, Eboda O, et al. 2014. Treatment of heterotopic ossification through remote ATP hydrolysis. Sci Transl Med 6:255ra132.
tion—an experimental antibiotic agent shows promising results in a murine model. Injury 44:570–575.

48. Seavey JG, Wheatley BM, Pavey GJ, et al. 2017. Early local delivery of vancomycin suppresses ectopic bone formation in a rat model of trauma-induced heterotopic ossification. J Orthop Res 35:2397–2406.

49. Chalidis B, Stengel D, Giannoudis PV. 2007. Early excision and late excision of heterotopic ossification after traumatic brain injury are equivalent: a systematic review of the literature. J Neurotrauma 24:1675–1686.

50. Ranganathan K, Loder S, Agarwal S, et al. 2015. Heterotopic ossification: basic-Science principles and clinical correlates. J Bone Joint Surg 97:1101–1111.

51. Reichel LM, Salisbury E, Moustoukas MJ, et al. 2014. Molecular mechanisms of heterotopic ossification. J Hand Surg 39:563–566.

52. Ramirez DM, Ramirez MR, Reginato AM, et al. 2014. Molecular and cellular mechanisms of heterotopic ossification. Histol Histopathol 29:1281–1285.

53. Downey J, Lauzier D, Kloen P, et al. 2015. Prospective heterotopic ossification progenitors in adult human skeletal muscle. Bone 71:164–170.

54. Lounov VY, Ramachandran R, Wosczyna MN, et al. 2009. Identification of progenitor cells that contribute to heterotopic skeletogenesis. J Bone Joint Surg 91:652–663.

55. Davies OG, Grover LM, Eisenstein N, et al. 2015. Identifying the cellular mechanisms leading to heterotopic ossification. Calcif Tissue Int 97:432–444.

56. Jackson WM, Aragon AB, Bulk-Hoover JD, et al. 2009. Putative heterotopic ossification progenitor cells derived from traumatized muscle. J Orthop Res 27:1645–1651.

57. Olmsted-Davis E, Gannon FH, Ozen M, et al. 2007. Hypoxic adipocytes pattern early heterotopic bone formation. Am J Pathol 170:620–632.

58. Dey D, Bagarova J, Hatsell SJ, et al. 2016. Two tissue-resident progenitor lineages drive distinct phenotypes of heterotopic ossification. Sci Transl Med 8:366ra163.

59. Forsberg JA, Potter BK, Polfer EM, et al. 2014. Do inflammatory markers portend heterotopic ossification and wound failure in combat wounds? Clin Orthop Rel Res 472:2845–2854.

60. Evans KN, Forsberg JA, Potter BK, et al. 2012. Inflammatory cytokine and chemokine expression is associated with heterotopic ossification in high-energy penetrating war injuries. J Orthop Trauma 26:e204–e213.

61. Peterson JR, De La Rosa S, Sun H, et al. 2014. Burn injury enhances bone formation in heterotopic ossification model. Ann Surg 259:993–998.

62. Giannoudis PV. 2003. Current concepts of the inflammatory response after major trauma: an update. Injury 34:397–404.

63. Vanzant EL, Lopez CM, Ozrazagt-Baslanti T, et al. 2014. Persistent inflammation, immunosuppression and catabolism syndrome after severe blunt trauma. J Trauma Acute Care Surg 76:21–30.

64. Nauth A, Giles E, Potter BK, et al. 2012. Heterotopic ossification in orthopaedic trauma. J Orthop Trauma 26:684–688.

65. Pavey GJ, Polfer EM, Nappo KE, et al. 2015. What risk factors predict recurrence of heterotopic ossification after excision in combat-related amputations? Clin Orthop Rel Res 473:2814–2824.

66. Evans KN, Potter BK, Brown TS, et al. 2014. Osteogenic gene expression correlates with development of heterotopic ossification in war wounds. Clin Orthop Rel Res 472:396–404.

67. Tannous O, Stall AC, Griffith C, et al. 2013. Heterotopic bone formation about the hip undergoes endochondral ossification: a rabbit model. Clin Orthop Rel Res 471:1584–1592.

68. Medici D, Olsen BR. 2012. The role of endothelial-mesenchymal transition in heterotopic ossification. J Bone Miner Res 27:1619–1622.

69. Dharm-Datta S, Etherington J, Mistlin A, et al. 2011. The outcome of British combat amputees in relation to military service. Injury 42:1362–1367.

70. Ladlow P, Phillip R, Etherington J, et al. 2015. Functional and mental health status of United Kingdom military amputees postrehabilitation. Arch Phys Med Rehabil 96:2048–2054.