**“Complex Regional Pain Syndrome (CRPS) in orthopaedics: an overview”**

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**Abstract**

Complex Regional Pain Syndrome (CRPS) is a debilitating, painful condition in a limb, occurring mainly after trauma and surgery, and associated with nerve, skin and bone abnormalities. The condition is poorly understood, often diagnosed late and national recommendations are not yet generally integrated into standard practice. Whilst signs and symptoms generally improve within six months of onset, many patients have long-term pain and disability, and the incumbent costs of managing chronic pain and disability are significant. This paper provides an overview of the latest understanding of CRPS and national guidelines, explains how to make a diagnosis, describes initial treatment and controversies in orthopaedic care and explores the implications of CRPS to the orthopaedic team.

**Key words** Complex Regional Pain Syndrome, CRPS, immune system.

**Conflicts of interest**

Then authors declare there are no conflicts of interest

**Introduction**

**Case Vignettes:**

Case 1

You review a 60 year old fit and healthy man at 5 weeks following nonoperative management of a simple distal radial fracture. He reports having felt “claustrophobic” in the cast from day 1 and have had the plaster changed on 3 occasions. On examination out of plaster, the patient has disproportionate pain, allodynia to light touch throughout the hand and he cannot make a full fist. There are no temperature or colour changes and the patient withdraws the hand every time you approach him. What will you do next?

Case 2

You have successfully performed a metatarsal osteotomy to treat hallux valgus in a 45 year old healthy woman. On review at 4 weeks, she complains of high intensity burning pain, and sensitivity throughout her foot and more limited foot and ankle movement than you would expect. Radiographs show mild localised osteoporosis around the MTPJ, and no signs of mechanical failure of fixation. On examination, there is mild mottled blueish discolouration throughout the foot, which also feels cooler than the other side. In general, she does not like anyone handling her foot. When you check the consent form, CRPS is not listed amongst possible complications. How will you inform your patient about her diagnosis?

**What is Complex Regional Pain Syndrome** **(CRPS)?**

CRPS is a debilitating, painful condition in a limb, associated with sensory, motor, autonomic, skin and bone abnormalities.1 CRPS replaces all other terminology such as ‘Sudeck’s Atrophy’, ‘Reflex Sympathetic Dystrophy’, ‘Algodystrophy’, ‘Fracture Disease’ and ‘Causalgia’, which are now considered outdated and misleading.2

CRPS often arises in orthopaedic practice, because orthopaedic doctors see patients after trauma or surgical intervention. Any trauma or operation to a limb, usually distal, can trigger CRPS; the type or magnitude of the trauma or surgery is of less importance.

Whether CRPS should be considered a rheumatic or a neurological disorder is not clear. With pain being the predominant issue, and in the absence of actual tissue destruction, CRPS is best classed as a “pain condition”, and though currently linked as a “focal autonomic disorder” in the WHO-ICD 11, this may be classified as one of the “primary chronic pains”.

**What causes CRPS?**

CRPS is a disease caused by post-traumatic regional hyper-activation of small nerve fibres. This abnormal nerve fibre activation leads to profound ‘central sensitisation’, a process in which the central nervous system (CNS) augments any peripheral impulses. We understand this role of the CNS from clinical studies involving low-dose ketamine treatment, which, by down-regulating central sensitisation can temporarily reduce CRPS pain, albeit with side effects.3

It is now clear that this nerve fibre hyper-activation is caused by an immune process in susceptible patients. Most patients with CRPS have specific autoantibodies in their serum, which upon transfer to hind limb-injured mice elicit a CRPS-like picture restricted to the injured paw, confirming an auto-immune origin.4 The pathogenetic antibody mechanism, or why patients produce these antibodies is yet unknown, but some genotypes are speculated to convey vulnerability.5,6

**Classification:**

Traditionally, two types of CRPS are described: Type 1 without, and Type 2 with a nerve injury typically caused by the same trauma that triggers the CRPS. For clarity, the nerve injury in Type 2 is not a consequence of CRPS.

The predominant management of both types is the same, and the distinction therefore has little benefit to a clinician.

**How common is CRPS?**

The incidence of CRPS in Europe is estimated as 20–26/100,000 person-years similar to the incidence of Rheumatoid Arthritis.7 CRPS has been reported as a relatively common occurrence, up to 32.2%, after wrist fractures,8 and a less common but recognised occurrence after foot and ankle surgery and joint arthroplasty. CRPS can occur within a few months of any limb injury or surgery; the incidence may have been overestimated in some published research when diagnostic criteria were not strictly applied;9 not every complex limb pain is CRPS (see making a diagnosis section).

Females (3:1 ratio), and patients with asthma, osteoporosis, migraines, or rheumatological disorders are at higher risk, as are patients taking ACE inhibitors.10 CRPS can rarely affect children and it sometimes affects adolescents.

CRPS can sometimes start in 2 limbs concomitantly, usually after bilateral limb trauma; in 5-10% of cases CRPS can spread to additional limbs, often without additional trauma.11

The overall socio-economic implications of CRPS are exorbitant. For example in Switzerland, the average overall cost of a distal radius fracture that is complicated by CRPS is about 25 times that of the costs of an uncomplicated fracture

**Making a Diagnosis**

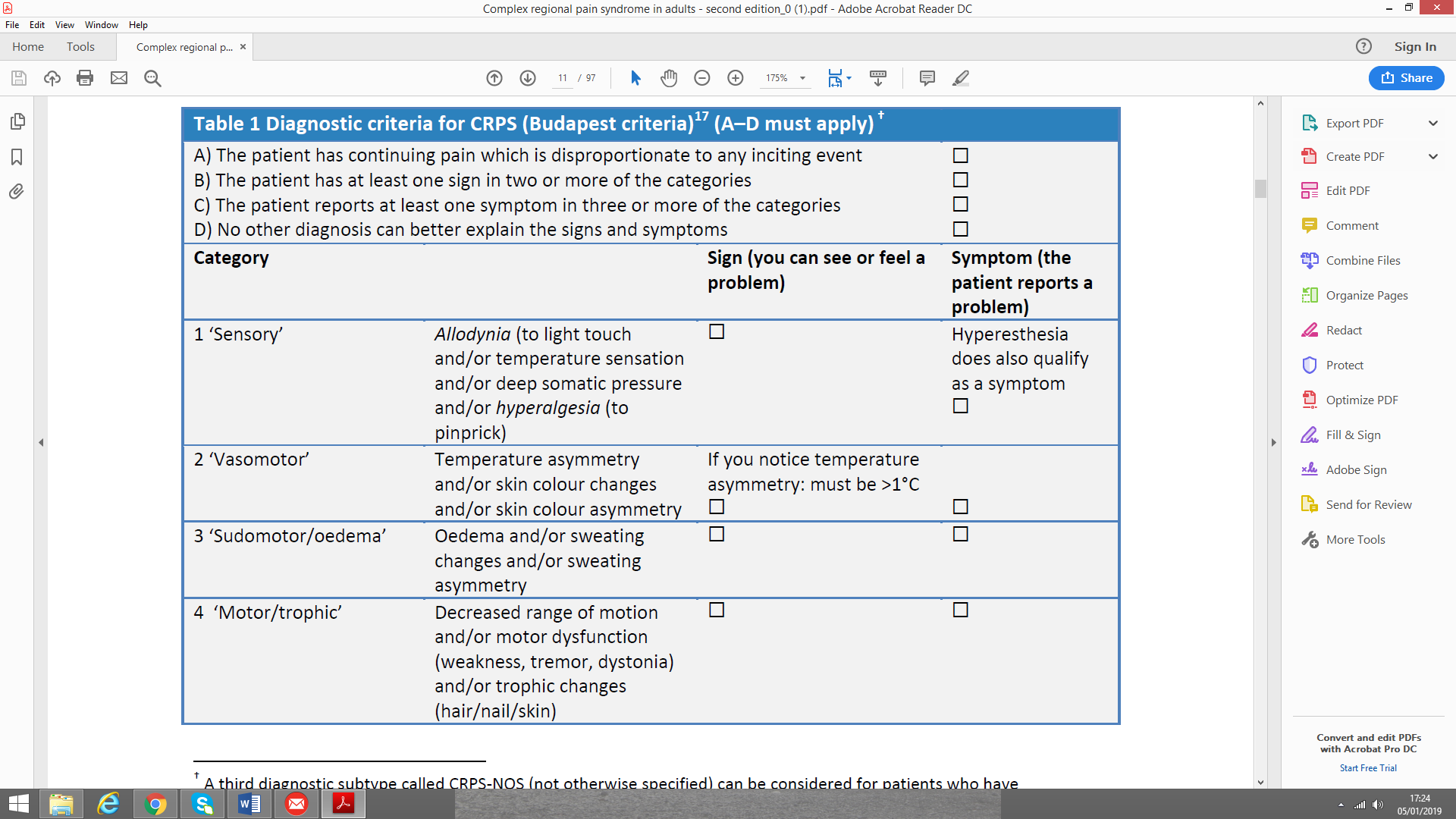
CRPS is a diagnosis of exclusion and the Budapest criteria (table 1)12 as adopted by the International Association for the Study of Pain (IASP) now supersede other criteria; their use is recommended in the UK.2 The use of a single set of diagnostic criteria allows consistency and a shared language.

The Budapest criteria identify symptoms and signs subdivided into four categories: i) sensory; ii) vasomotor; iii) sudomotor/oedema and iv) motor/trophic. Other conditions, such as infection, failure of fixation, nerve compression or malignancy may have some features of CRPS and should therefore be carefully excluded. Fortunately, in orthopaedic practice, patients often have ‘barn door CRPS’, readily identifiable using the Budapest criteria. If an orthopaedic surgeon does not feel confident to diagnose CRPS, then it is reasonable to ask a pain specialist to verify the diagnosis.

Signs such as swelling, sweating, colour and temperature changes, and hair/nail growth changes generally reduce with time, although pain and motor symptoms can persist longer. Theoretically, a diagnosis of CRPS according to the Budapest criteria cannot be upheld once patients who earlier had documented limb signs have lost their visible signs, but in practice this situation is rare as most patients retain their motor and sensory signs and report additional symptoms (table 1). A reduction of signs is in itself not defined as ‘recovery’. Where pain persists, the condition is considered to be still active.

A more challenging scenario is where patients never received a Budapest diagnosis and their clinical signs are never documented by a healthcare professional. Earlier diagnostic criteria for CRPS were looser, and the presence of fewer signs, or indeed the report of symptoms only was acceptable. A specific category has been created to somehow capture these patients (CRPS-not otherwise specified, NOS). The diagnostic specificity and sensitivity of CRPS-NOS is poor - no research has been conducted in this group - this category is best avoided in orthopaedic practice.

The physical signs and symptoms of CRPS distinguish it from other neuropathic pain problems. The prognosis may also be different, and care should be taken to recognise this early.



*Additional symptoms*

Many patients with CRPS have a constellation of additional symptoms not included in the Budapest criteria. These symptoms are often difficult for patients to explain, and are best summarised as ‘neglect-like’. Typically, patients experience their limb as being different in size or shape, or in a spatial location from what it really is. Patients also develop an abnormal cognitive/emotional relationship with their limb, characterised by alienation, dislike and disgust, anger and neglect, and some may even have a wish for immediate amputation. These symptoms, likely caused by a shifted representation of the affected limb in the sensory cortex,13 are transiently present more often after any limb injury than clinicians may recognise,14 but are even more common and more long-lasting in CRPS. These symptoms are bewildering and distressing; patients may fear they ‘go mad’, or that they are not being believed. This fear can lead to lack of communication, and It can be salutary if the healthcare professional signals that they understand what their patient goes through.

**Management of CRPS**

The British Orthopaedic Association15 recommends early diagnosis and an agreed care pathway for patients with CRPS, as do the Royal College of Physicians (RCP).2

Perhaps one of the most useful and simple interventions is to ensure there is at least one “CRPS champion” within any practice area. This position has been successfully established in some UK clinics as part of their acute CRPS care pathways, and a physiotherapist may often be ideally placed to undertake this role.16 The CRPS champion’s role is to keep the team updated with evidence-based practice, being the “go to” person when CRPS is suspected, and acting as a link between different professionals involved in patient care to ensure care pathways are effective.

A four-pillared management approach is recommended: this includes pain relief; physical and vocational rehabilitation; patient information and education to support self-management; and psychological intervention. The first 3 pillars can be delivered in orthopaedic practice.2

*Pain Relief:* A protocol for first line medication should be agreed locally and generally include simple analgesia including weak opiates, with the addition of neuropathic pain medication from 3-4 weeks, or sometimes earlier, to facilitate rehabilitation. A sample protocol is provided in the orthopaedic section of the UK Guidelines (*Figure 1*). While there is little evidence that these medications are effective in reducing the actual CRPS pain, they might treat secondary musculoskeletal pains. The individual response should be assessed repeatedly, and medications stopped if found ineffective.

Figure 1



*Physical and Vocational Rehabilitation:* Early referral to physiotherapy and /or occupational therapy (PT/OT) is vital. For simple cases PT/OT will be the most important intervention required, especially if there is expertise and experience within the therapies department. Prolonged immobilisation and reducing functional activity as a treatment are not recommended and may be harmful even though this may feel intuitively right when a patient has had a fracture. General guidance is to only immobilise if necessary and not beyond the normal timescale for the particular injury. Early function, attention to the injured limb and gentle exercise should be encouraged from first contact. Interestingly, the benefits of this important management strategy can be modelled in rodents, where painful sensitivity after tibia fracture lasts much longer if the fractured and stabilized limbs are being immobilized.

There are a number of novel physical therapies such as graded motor imagery and mirror visual feedback that can help patients with CRPS; all therapies are focussed on restoring function as soon as possible to normalise the sensory-motor feedback loop.

*Patient Information and Education:* Many patients will utilise the internet and social media following their initial diagnosis, and may see horrible stories representing extreme subtypes. It is important to reassure patients that the difficult-to-bear initial pain will in all likelihood improve, and that they can help their progress by adhering to gentle physiotherapy. Information should therefore include the usually benign nature of the condition.

*Other methods of treatment:* Blockade of interleukin-1 will prevent or revert transferred CRPS (‘tCRPS’) in mice, indicating that immune treatments may also be of use in treating patients, and this is an area of ongoing research interest

Research evidence does not support local or regional blocks as a treatment for CRPS

**What is the typical disease course?**

About 80% of patients with CRPS will get substantially better within the first six to twelve months after trauma due to a natural resolution process. However they often report lesser ongoing pain or partial loss of function for many years, and only about a third of patients consider themselves fully recovered at six years.7 15-20% of patients will have persistent symptoms for many years and may never fully recover.17

It is not yet possible to clinically predict how patients will recover, however it is likely that this rare latter group of patients that don’t recover at all has fundamentally a different disease, which cannot be prevented or shortened even with excellent early treatment.

Rarely, patients can present with ‘relapsing-recurring’ CRPS, with remission periods varying between months and years.1

Since early rehabilitation in established CRPS very likely shortens the disease course, a late diagnosis contributes to a protracted course.

**Uncommon subgroups of CRPS**

About 10% of patients with persistent CRPS may develop widespread pain, which may have in some a neuropathic character similar as the pain in the originally affected limb, or alternatively such widespread pain can also have a musculoskeletal character such as in fibromyalgia syndrome. One other, peculiar, rare presentation is the ‘shoulder-hand syndrome’, with neuropathic pain and sensitivity in the shoulder, and typical CRPS signs, but usually no pain, in the ipsilateral hand.

Some patients develop tremors or myocloni in the affected limb, or occasionally fixed dystonia.

Some patients develop small blisters which spontaneously erupt, and then heal; others can develop skin ulcerations which get infected requiring antibiotic treatment.

Orthopaedic surgeons must be aware of the existence of these subgroups, and support patient management by recognising the need for onward referral.

**Can CRPS be prevented?**

There is preliminary, but persuasive evidence that CRPS after a wrist fracture is often preventable by establishing early, simple rehabilitative measures.16 In animal fracture models, those animals which exercise early recover earlier and have less pain; this is likely mediated through exercise-induced anti-inflammatory effects. Maintaining normal sensory-motor feedback loops may also help to maintain representation in sensorimotor cortex and help prevent central sensitisation.

Tight or restrictive plasters and disproportionate pain beyond a few days from injury/ surgery are well recognised as risk factors for CRPS. When these occur, they should be addressed as soon as possible (See Box 1.)

**Box 1 Key elements of successful CRPS preventative intervention in orthopaedics**

1. Do not immobilise excessively or unnecessarily
2. Ensure casts/ splints or boots are well fitting and comfortable, avoid over-flexion of wrist in cast, smooth sharp edges and ensure there is no restriction to unaffected joints
3. Encourage patient to return to clinic if any concerns
4. Encourage hourly gentle exercises to control swelling in elevation e.g. grip-release, toe flexion/ extension
5. Encourage light function and attention to limb whilst in cast/splint or boot
6. All verbal information given should be supported with a patient information leaflet and visual reminders such as posters in clinics to help reinforce points 2, 3, 4 and 5
7. All advice given should be recorded in patient notes
8. Recognise “at risk patients” e.g. high pain beyond a few days and /or lack of engagement with limb
9. Patients reporting tight and/ or restrictive casts should **always** have this cast changed
10. Patients requesting repeated change of cast or reporting “claustrophobia in cast” should trigger immediate referral to specialist physiotherapist within clinic

**Psychological aspects of CRPS**

Several decades ago the existence of a ‘CRPS personality’ was proposed, but this is now obsolete18 and current evidence suggests that psychological distress is generally not a risk factor for the development of CRPS. Having CRPS, as with any severe chronic pain is stressful and many patients will develop secondary psychological co-morbidity such as anxiety or depression. This should be recognised and treated as with any other condition (e.g. depression in a patient with diabetes).

Whether or not psychological factors constitute a risk in CRPS-subgroups, or contribute to the perpetuation of CRPS has not yet been clarified.

Rarely people self-induce signs with the aim of making their limb appear as though they have CRPS. Methods have been described19 and clinicians should be cautious of this. While such actions may occasionally be employed to gain benefits in a medico-legal context, in very rare cases serious psychiatric ‘factitious disorder’, may be present, where patients create symptoms to gain medical attention.

**Surgery in patients with CRPS**

*Operating on a CRPS-affected limb*

Elective surgery on a limb previously affected by CRPS should be delayed where possible until acute signs of CRPS have clearly improved and stabilised. Waiting for a period of a year after the CRPS onset should generally achieve this. Based on the limited evidence available, it is thought that the rate of operation-triggered recurrence of CRPS is <15%, with most recurrent cases being mild.20,21 If surgery on an affected limb is unavoidable, this should ideally be performed by a surgeon with experience in operating on patients with CRPS with an anaesthetist who is also a pain specialist, and patients should be told about the risks involved.

*Operating in a non-CRPS affected area in a patient with a history of CRPS*

There is a dearth of high-quality evidence in this area. Anecdotal reports suggested that complications such as poor wound healing following orthopaedic surgery in patients with CRPS may be more common, even if conducted in unaffected areas.

Some recent evidence suggests that patients with a history of CRPS may be at higher risk to develop CRPS following operations in previously non-affected limbs.22 However, this should be regarded as preliminary, and it is important that such preliminary results do not indiscriminately scare surgeons from performing otherwise useful operations. Patients should however clearly be counselled about their potentially higher risks.

*Amputation to reduce pain or to improve function from CRPS*

Orthopaedic surgeons may be asked to perform amputations for chronic CRPS due to pain, deformity or chronic infection secondary to CRPS. This area is extremely complex, and multidisciplinary input is mandatory.

Based on current evidence, the RCP CRPS guidelines2 does not recommend amputation, but recognising the importance of patient autonomy and the pressure sometimes applied to surgeons, offers detailed guidance for those referred for amputation and for those planning amputation.

The decision to refer should be made by a multidisciplinary expert team including a pain specialist, pain-psychologist, and a pain specialist physiotherapist. The referral should always be to a tertiary rehabilitation team with experience in this area, and not to a single-surgeon service. Patients and their families should be made aware that the amputation is unlikely to resolve their pain, and that CRPS may recur in the stump or in another limb, and prosthesis use may not be possible. Amputation may be considered in cases of intractable infection of the affected limb that cannot be controlled with antibiotics. Except in immediate emergencies, involvement of the outlined multidisciplinary teams is essential, and patients should be made aware that ulceration might recur in the stump after amputation.

*Operating to reduce nerve compression in a patient with CRPS type II*

There is preliminary evidence that surgery for neuropathic pain attributed to nerve compression (confirmed by nerve conduction studies) might also improve CRPS symptoms in the distribution of that nerve.23

*Are patients with a chronic pain condition other than CRPS more likely to develop CRPS after elective limb surgery?*

This is a complex area, which is outside the scope of this review. The issues include: i) is elective limb surgery planned mainly aiming at reducing pain? ii) did the patient have past operations aiming to reduce their pain? iii) does the patient suffer from other chronic pains?

Pragmatically, it is our opinion, that assessment before elective orthopaedic limb surgery with the main indication of reducing pain should include an assessment for other chronic pains, and a clear recognition of the outcomes of any previous elective operations aiming to reduce pain. Patients may, for example suffer from other types of chronic pain, such as fibromyalgia, a common widespread pain condition (2-8% of the population affected) which is associated with other symptoms such as irritable bowel and fatigue. We anticipate that the routine assessment for, and recognition of these issues will lead orthopaedic surgeons to develop their practice over time as appropriate.

**Informed consent and shared decision making**

Since CRPS is rare and can be devastating, it is a prime example of those conditions which since the Montgomery ruling deserves renewed consideration as a material risk.24 It appears now rarely acceptable to not explain this risk in some detail, or to assume that the patient understands the implications when they are told this only at the day of the operation.

While explaining the risk and sequelae of CRPS is always important, it is perhaps even more urgent with potential aggravating factors such as previous CRPS or concomitant chronic pain states. Patients do not always volunteer information about their past pain history and it is the responsibility of a surgeon to seek this relevant information. Close questioning about the medications a patient is currently prescribed can also point to undisclosed chronic pain conditions, and the need for appropriate counselling.

In patients who develop CRPS following surgical intervention for acute trauma, it is difficult to determine which event – the trauma or the surgery – accounted for the development of the CRPS. Patients should be counselled that both events are risk factors for CRPS.

Finally, it is worth noting that a surgeon is not to blame if a patient develops CRPS - it is an expected risk, though a patient may not perceive it in that way. The importance of informed consent therefore cannot be stressed enough.

We would also suggest from anecdotal evidence that as recent information about the beneficial effects of early rehabilitation16 filters through into the medicolegal system, there will be an increasing number of cases claiming damages from delayed or inadequate functional rehabilitation following surgery or trauma.

**Case Vignettes:**

**Answers**

Case 1

The patient has a number of risk factors for CRPS i.e. recent injury, feeling “claustrophobic” in cast, a number of plaster changes and a fear of touch. He fulfils category A, B and probably D but not category C in the Budapest CRPS Diagnostic Criteria. Following current guidelines, he does not fully fit the diagnostic criteria for CRPS. Current evidence suggests immediate referral for PT/OT and review of medication to facilitate rehabilitation. It cannot be predicted if he will progress to fulfil the diagnostic criteria for CRPS so a further review is recommended within a month to monitor effect and adjust medication. Communication with GP is essential to facilitate timely titrating appropriate analgesia and to consider neuropathic pain medication if needed. Making the GP aware of RCP CRPS guidelines can be helpful. If there is no progress onward referral to a pain specialist within three months of onset is recommended.

Case 2

The patient has had a trauma (surgery) which puts her at risk of CRPS. She fulfils category A, B, C and D and therefore meets the Budapest CRPS Diagnostic Criteria (Table 1). It is important to acknowledge your concerns with the patient in a manner which does not heighten fear, anxiety and apprehension. Failure to list CRPS in the list of complications should be acknowledged as full and honest disclosure to the patient. At this stage there is good reason to believe that with appropriate PT/OT and medication to facilitate rehabilitation it is most likely her symptoms will improve. Normalising function is the goal. It is also important to explain that only a few go on to have long lasting pain and reduced function despite the appropriate therapy.

**Box 2 Top tips for an orthopaedic surgeon regarding CRPS**

1. Include CRPS as a potential complication when counselling patients for surgery or after injury.
2. Recognise “at risk” patients in trauma and elective practice, and learn to recognise the early signs and symptoms of CRPS.
3. Use the Budapest diagnostic criteria: put a poster on the wall in your clinic as a visual reminder
4. Foster “CRPS champions” in your practice: these may be physiotherapists or other health care professionals who can support care pathways and keep the team updated
5. Design a care pathway to meet BOAST standards for patients with early CRPS within your fracture and elective clinic practice. If you are commissioned to provide care you are commissioned to provide appropriate care pathways.
6. Institute early referrals to physiotherapy and the pain team and agree first line medications for CRPS locally
7. Use the RCP CRPS guidelines to inform best practice

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