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Pain in the patient with an orthopedic infection during diagnosis and treatment

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Summary

Pain can be thought to be the result of the brain's response to tissue damage: this may lead to attribute a simplistic nature to pain. In reality, sensory, cognitive, and affective processes all influence the subjective experience of pain which therefore assumes substantially more complex characteristics: there is therefore a concrete potential for diagnostic or therapeutic error deriving from a fallacious global evaluation of pain. Some key concepts, based on literature data rather than on clinical experiences, are outlined. First, the need to not underestimate pain as possible first expression of an infectious problem. Also, given the need to guarantee patients appropriate pain treatment, evidence on multimodal analgesia in acute pain (drug therapy, non-drug therapy, anesthesia), up to multidisciplinary approaches (with a neurologist, psychiatrist, physiatrist, etc.) in chronic pain have been reviewed.

Key words: pain therapy, infections, orthopedic surgery, osteosynthesis, arthroplasty

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Introduction

To outline the aspects relating to pain and its role in the management of infectious diseases in the orthopedic field, it is first useful to define pain. Over the course of history, not only in medicine, the most varied definitions of pain have followed one another, from those of a more "philosophical" nature, such as the idea, born in the nineteenth century, that pain is an evolutionary mechanism aimed to protect the organism from damage, to the more technical ones, for which pain is "an altered brain state in which functional connections are modified, with components of degenerative aspects" [1]. In the 1970s, the IASP (International Association for the Study of Pain) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of damage" [2]: this was ultimately the definition adopted by the World Health Organization. It can therefore be affirmed, in the first instance, that pain is the result of the brain's response to tissue damage. This assumption may lead to attribute a simplistic nature to pain and at least this has happened historically: the IASP definition specifies how sensory, cognitive and affective processes influence the subjective experience of pain, which therefore assumes substantially more complex characteristics than the mere response to tissue damage [1].

In fact, pain is a highly individualized experience, in which differences between subjects lead to significant sensory variations and, consequently, in the expression of the symptom: there is therefore a concrete potential for diagnostic or therapeutic error deriving from a fallacious global evaluation of pain [3]. It is the clinician's task to approach any path of diagnosis and treatment with sufficient skill in assessing

(qualitatively and quantitatively) the pain symptoms reported by the patient: the management of patients suffering from osteoarticular infection is no exception.

Precisely for this purpose, a brief excursus on the classification and pathophysiology of pain will be useful.

The symptom "pain" can be classified according to numerous factors: temporal (acute, subacute, chronic); modal (e.g., intermittent, stabbing, burning, etc.); mechanistic (nociceptive, neuropathic); diagnostic (e.g., oncological, vascular, arthritic, etc.); anatomical (e.g., headache, back pain, abdominal pain, etc.); topographical (central or peripheral); etc. [4]. Probably the first and simplest classifications, closely connected, are the temporal one and the one based on the mechanism of onset. Based on these, pain can be dichotomized into two categories: acute/persistent, if lasting less than six months, or chronic beyond this duration, in which the first is usually associated with pathological condition, while the second can also persist following the resolution of the same [5] (Tab. I).

According to the modal classification, there are essentially two types of pain: nociceptive pain, which arises as a result of the activation of skin or soft tissue nociceptors induced by an injury, and can be of variable intensity; neuropathic pain, caused by damage or dysfunction of the nerve fibers, which manifests itself as a burning or dysesthesia sensation [7], a characteristic that unites it with the main forms of chronic pain.

To understand the reasons for this heterogeneity of clinical manifestations, it is useful to remember the anatomo-functional basis of pain perception.

The afferent signals coming from the periphery are essentially transmitted through three types of nerve fibers: Aβ fibers, myelinated with a large diameter, characterized by high transmission speeds; Aδ fibers, myelinated with a small diameter, intermediate speed; C fibers, unmyelinated with a small diameter and low transmission speed [7,8]. Harmful stimuli activate different types of nociceptors, in turn associated with different classes of nerve fibers: thermal and mechanical nociceptors transmit their signals through relatively fast fibers (Aδ); however, there are also polymodal nociceptors, which are bound to low-speed unmyelinated type C fibers. The Aβ fibers, on the other hand, are mainly involved in the transmission of tactile sensitivity: as explained later, however, they have a crucial role in the modulation of the nociceptive signal [8].

From a biochemical point of view, the C fibers release substances that are capable of modulating transmission of the signal: in particular, substance P increases and prolongs the effect of the neurotransmitter glutamate, which is involved, among other things, in the transmission of the tactile and pain signal: there are mechanisms for reabsorption of glutamate, while their existence has not been demonstrated for substance P or other neuropeptides, which therefore have characteristics of persistence and diffusion at the level of the surrounding nerve cells: it is thought that this contributes to the diffuse character and hyper-excitability characteristics of many pain syndromes [7].

There are numerous systems that are capable of modulating painful sensitivity (even to the point of cancelling it): for example, the presence of inhibitory interneurons at the level of the spinal cord is at the origin of the "gate control" theory, according to which the activation of non-nociceptive afferences through Aβ fibers causes the closing of the "gate" and consequent blocking of the central transmission of the painful stimulus (the electrical stimulation techniques for pain therapy are based on this principle) [7]. Another important discovery in the knowledge of the mechanisms of pain transmission is that which demonstrated the presence of "descending" control pathways of central origin. These descending pathways respond in turn to electrostimulation by blocking painful symptoms: it seems that the effect of opioids is also mediated by the activation of these pathways, which are also stimulated through opioid receptors by stressful situations by release of endorphins [7]. Furthermore, the presence of "excitatory" de-

Table I. Difference between acute and chronic pain (from Varshney et al., 2016) [6].

Characteristics	Acute pain	Chronic pain
Temporal features	Short history of onset and does not last longer than days or weeks	Long history with often poorly-defined onset; duration unknown
Intensity	Variable	Variable
Associated effects	If pain is severe anxiety may be prominent and sometime irritability	Depression and irritability is prominent feature
Associated pain behaviors	When pain is severe pain behaviors (e.g. moaning, rubbing and splinting) may be prominent features	Specific behavior may or may not be present. If pain is severe and for long duration specific behaviors (e.g. assuming a comfortable position) may occur
Other associated features	Features of sympathetic hyperactivity when pain is severe (e.g. tachycardia, hypertension, sweating, mydriasis)	Usually have one or more vegetative signs such as lassitude, anorexia, weight loss, insomnia, loss of libido. Sometimes these signs may be difficult to distinguish from other disease-related effects

scending mechanisms has also been demonstrated: this is also an important aspect that is capable of explaining the extreme subjectivity of painful sensitivity [8].
Finally, as already mentioned, the perception of pain is strongly influenced by psychological and emotional factors: for example, knowing that you have an infection can exacerbate the sensation experienced by the patient due to anxiety/stress/fear or the presence of exudate/bad smell [3]. Once, in fact, that the painful signal, suitably modulated in an excitatory or inhibitory way (when not completely inhibited), is finally transmitted to the brain, it is in turn subject to further connections that modify its perception: in particular, four brain areas activated by pain have been identified, two of which are mainly involved in the sensory discrimination of pain, and the remaining ones implicated in emotional and affective aspects.
For the clinician, these notions are a source of complexity in the diagnostic approach to the patient who complains of joint pain, especially if in the post-operative period of prosthetic surgery: however, they are also an important therapeutic target in treatment algorithms which must be, as indicated below, necessarily "multimodal".

Pain as a symptom

Characterizing pain in post-surgical infections has important repercussions on the diagnostic path. In fact, pain is often the first warning in a surgical site infection. From a pathophysiological point of view, the mechanisms responsible have not yet been fully clarified. Traditionally, pain was thought to be due to inflammation caused by pathogens: however, the recent discovery that nociceptors can be activated directly by microorganisms has led to other and more fascinating hypotheses. In fact, it has been shown that, for example, the alpha hemolysin produced by *S. aureus* can create pores on the membrane of nociceptors causing transmission of the painful stimulus, but pain-inducing substances are substantially produced by each type of pathogen, whether gram positive or negative, as well as viral particles or fungi [9].
It is thought that pain in response to infections is an evolutionary mechanism developed by the organism to fight invasion more effectively (it is known, in fact, that the neuropeptides mediators of the pain stimulus have an important immune role): however, the opposite hypothesis, according to which this type of pathogen-mediated activation is a factor that promotes the virulence of the infection, has been proposed [9]. Indeed, further studies are needed to clarify these aspects: the fact remains that, as is known and previously reported, pain is an early and prevalent feature of most infections [9].
All diagnostic algorithms, in fact, in suspecting an infection, start from the pain symptom, as well as from the rarer presence of a fistula or secretion, as a reason that in itself justifies the execution of tests aimed at excluding an infectious picture (e.g., C-reactive protein, cultures, imaging, etc.) [9,10]. Infection-related pain is usually described in fairly typical terms (localized pain in the surgical area, throbbing, rarely constant throughout the day) [3].
In fact, facing a painful prosthesis, infection is an event that must primarly be taken into consideration [10]: this is true both in the case of painful prostheses right from the immediate post-operative period, in which the pain can be caused by an early infection, as well as when pain develops after months or years [11]. An important feature is the fact that pain from infection is often referred to as "different" from the usual perceived pain [3]. Therefore, it is useful to treat any "new" pain as suspicious for an infection, especially when approaching a patient with a chronic painful prosthesis for which a septic problem had already been excluded in the past: the changed characteristics of pain may be a sign of a previously absent infection.
In the literature, different classification systems have been proposed for prosthetic infections, which are based on the timing of biofilm formation and/or on the topographical extension of the phenomenon at the tissue level. Simplifying, the fundamental distinction is between early (< 4 weeks) or delayed (1-24 months) infections, in which the acquisition of the pathogen is assumed during surgery, and late infections (> 24 months), in which it is believed that the hematogenic pathway predominates. In each of these clinical pictures, the pain has different characteristics that can help in the diagnostic process, inducing, in relation to the timing of onset, suspicion of an ongoing complication.
More specifically, the clinical pictures that are highlighted are an "acute" picture, which can gather early and late hematogenous infections [12], in which, as in superficial infections, the classic signs of inflammation are present and the pain is typically localized and throbbing, frankly "nociceptive" [11,12]. The "chronic" type pictures, typical of delayed infections with scarcely virulent pathogens, have more challenging clinical characteristics from a diagnostic point of view. In these cases, the appearance of the wound is often deceptive, and the signs of infection can be mild [11]. The pain can have the characteristics of chronic pain or be absent, to the point that, with regards to the knee, in some cases the clinical suspicion is to be posed only in relation to an ensuing reduction of range of motion [11,13].
With regards to post-surgical infections in trauma, the literature is even more scarce, although it is useful to underline some peculiarities. First of all, classification: although there is, also in this case, a distinction based on the timing of onset (early or late infections), the biomechanical aspects (stability of synthesis/callus) have a specific importance. Contrary to what occurs in prosthetic surgery, in traumatology it is possible to proceed with the definitive removal of the hardware (with the consequent obvious benefits in prognostic terms) as soon as the fracture has healed, which is why a special classification system has been proposed [14,15]. From a diagnostic point of view, in early infections the clinical picture is often frankly suggestive, since the classic signs of inflammation are present; on the

other hand, in delayed infections, which are usually due to less virulent microorganisms, symptoms can be more vague. In relation to this, it is always necessary to suspect the presence of a late infection in cases of delayed consolidation, pseudarthrosis, or hardware loosening [14,16]. From a general point of view, in the absence of specific protocols on pain management in the complications of internal fixation, we recommend excluding the presence of an infection whenever a new onset of pain or a modification of the usually perceived discomfort develops in a patient who sustained fracture osteosynthesis in the past (Figs. 1 and 2, septic complications after osteosynthesis).

Pain as a therapeutic target

Studies on pain in patients with chronic wounds have shown that various aspects of the quality of life can be negatively affected by pain, such as interpersonal relationships, work, social activities and emotional well-being [3]. It is therefore mandatory to treat pain correctly in the management of a patient with an infection. From a therapeutic point of view, much progress have been made over the years in the management of severe pain, to the point that pain therapy has become a highly specialized field. There is no evidence that leads one to believe that dissimilar management of pain therapy is necessary in orthopedic infections compared to pain from other causes.
The first step is evaluation: the symptoms must be investigated regularly to monitor pain over time. Over the years, several quantitative and qualitative assessment tools have been developed and validated to measure baseline pain and changes over time [3,17]. As already described, in fact, there is not just one type of pain. Simplifying as much as possible, in fact, this can be nociceptive or neuropathic, acute or chronic. It is important, in management, to be able to correctly identify the type of pain that one is facing and to understand the evolution of pain over time [3,6]. As mentioned, acute pain, typical of early or late hematogenous infections, is sudden and localized, having the function of informing the subject of a condition of current or potential damage, while chronic pain develops insidiously, it can be intermittent or persistent and has the characteristic of being able to persist even when the damaging stimulus has been removed [6]. This introduces a "sensitization" mechanism, whereby nociceptors located in the vicinity of the area stimulated by injurious mechanisms, which were previously insensitive to the aforementioned, begin to respond. It is thought that this phenomenon is due to the release of various chemical substances by the injured cells and surrounding tissues (bradykinin, histamine, prostaglandins, leukotrienes, acetylcholine, serotonin, substance P). Moreover, these mediators have been shown to autonomously support the inflammatory response, which is therefore called "neurogenic" inflammation [7]. In addition to this, there is another type of sensitization, the so-called central sensitization, which acts by means of synaptic plasticity mechanisms on the other control mechanisms intrinsic in the transmission system of pain

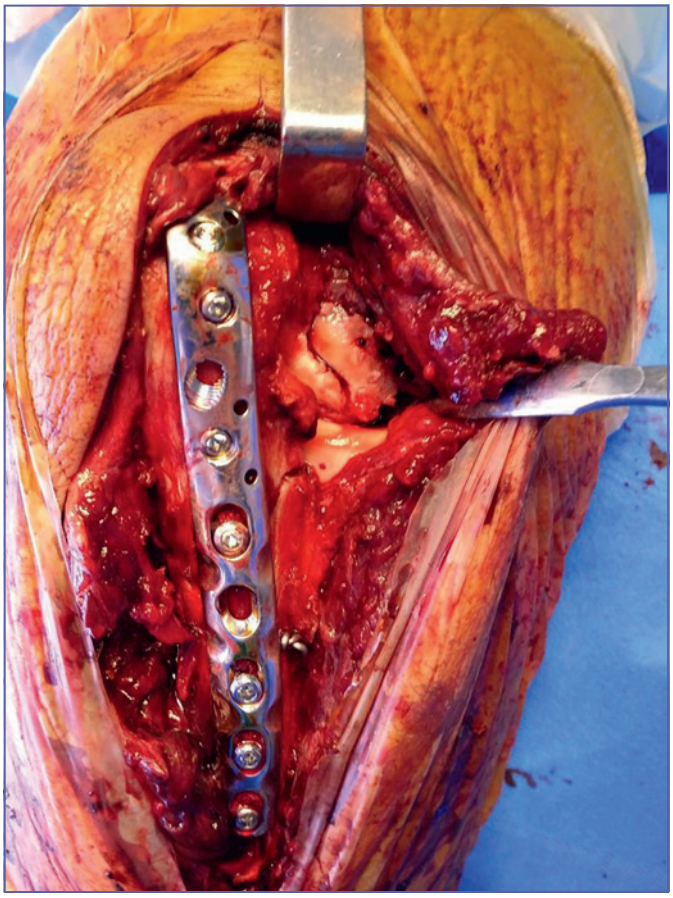

Figure 1. Surgical treatment of deep infection after osteosynthesis.

sensitivity, at the level of the central nervous system (see the introduction, "Descending ways"). This phenomenon has profound clinical implications, being the main therapeutic target of strategies aimed at preventing the onset of chronic pain [6].

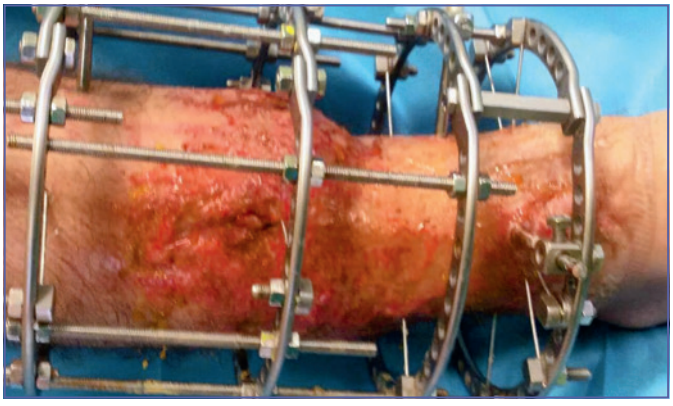

Figure 2. Superficial infection after exposed fracture treated with circular external fixator.

In fact, it has been shown that poorly controlled pain has various negative effects on the body: increased sympathetic response with consequent tachycardia and cardiac and metabolic fatigue, increased thromboembolic risk, and gastrointestinal and urinary problems, up to psychological changes (anxiety, depression, insomnia, existential distress) [6]; last but not least, it seems that pain also negatively affects the healing processes [3,6]. Acute pain that is not treated promptly and adequately leads to chronic pain, precisely by virtue of the sensitization processes [6]. For this reason, it is essential to correctly manage acute pain immediately using all the tools available: it is now established that the best strategy for pain management, aimed at maximizing lasting efficacy by limiting as much as possible side effects and adverse events, is the use of multimodal analgesia [6,18]. It consists in the use of two or more different analgesic techniques, pharmacological or non-pharmacological. Below is a brief overview of the various therapies available, the choice of which is based on the individual characteristics of the patient, as well as according to the expertise present at each specific center.

First of all, as the cornerstone of analgesic therapy, pharmacological therapy should be reported. Rather than a list of drugs available, it is useful to remember how, since 1986, the WHO has been promoting the "pain ladder" for the choice of drug therapy for pain. The fundamental principle is that the drug should be taken with the simplest possible route of administration (e.g., by mouth), on a regular basis (e.g., at fixed times), in accordance with the type and intensity of pain, and if possible, in self-administration [17]. Specifically, the "ladder" provides that any therapy should be prescribed progressively, starting initially with non-opioid drugs (paracetamol and NSAIDs), moving on to stronger therapies (weak and then strong opiates) if adequate efficacy is not achieved, taking care to trim down the therapy ("go down the ladder") if the existing one becomes excessive with the progress of the clinical course. Essential, at any step of the ladder, is the use of adjuvant therapies such as antidepressants, muscle relaxants, and sedatives in relation to the specific picture of the individual patient [6,17]. In the infectious field, of course, any therapy must be associated with the correct antibiotic treatment for the underlying disease, where applicable [3].

In addition to drug therapy, other treatments can be part of an integrated multimodal treatment. Among these are non-drug treatments such as physical therapies, cryotherapy, heat therapy, etc.; minimally invasive procedures on the nerves by anesthetic block, radiofrequency, alcoholization; actual neurosurgical procedures. It is the pain therapist's task to create the right balance between pharmacological and non-pharmacological treatments and procedures in order to interrupt the sensitization cascade and avoid chronic pain, minimizing the negative effects of each therapy [17].

In addition to multimodal analgesia, in severe cases in which chronic pain is already build up, which as such endures regardless of the persistence of the underlying condition, the use of multidisciplinary analgesia is warranted. This type of approach is based on Engel's biopsychosocial model, according to which chronic pain is a pattern of psychophysiological behavior that cannot be divided into distinct psychological or physiological components, for which the treatment must necessarily take into consideration both physiological and psychological and social aspects [19]. In practice, this is obtained with the creation of teams dedicated to pain management, which include a pain therapist, neurologist, psychiatrist, physiatrist, physiotherapist, etc. [17]. In the case of osteoarticular infections, it seems wise to propose that figures such as the orthopedic surgeon and the infectious disease specialist are also included in the multidisciplinary team. These models have been successfully tested in Belgium and then spread to other contexts, and allow patients to benefit from the coordination of various specialists (usually directed by the pain therapist), thus increasing the chances of receiving timely and accurate diagnoses by benefiting from various specifically developed therapies according to their individual needs [17,19].

Conclusions

In the literature, there are very few specific articles on the topic of pain management in patients with osteoarticular infection. This is surprising as there are many patients suffering from septic complications, who face important and disabling painful symptoms, which are associated with other functional and social problems related to these illnesses and which, therefore, often end up resulting in chronic pain syndromes.

The objective of this brief review was to outline some key concepts, based on literature data rather than on clinical experience, which may be useful for daily practice in centers that are not specifically dedicated to the management of infectious orthopedic problems. First, the need to not underestimate pain as a possible first expression of an infectious problem.

Even from the point of view of management in the infectious disease field, the correct approach passes from scrupulous quantitative and qualitative assessment of the painful situation. It is necessary that, even in first level centers, there is the knowledge and structures necessary to guarantee patients a therapy that is modeled correctly around the individual subject, in a multimodal way even in acute pain (drug therapy, non-drug therapy, anesthesia), and up to multidisciplinary approaches (with neurologist, psychiatrist, physiatrist, etc.) in chronic pain.

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Authors' contributions
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Ethical consideration
The study is based on mere literature data therefore nor ethical committee approval neither informed consents were acquired.

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