

The pain in the Emergency Department: Choosing and treating wisely before and during the COVID-19 era

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Abstract

Pain is a frequent reason for referral to the Emergency Department (ED). Adequate management of pain is a moral and ethical imperative. If not correctly treated, acute pain can cause physical and psychological complications, and become chronic with severe consequences such as anxiety, depression, and social isolation. As consequence, emergency clinicians should treat pain as soon as possible, avoiding delays even in case of acute abdominal pain. Pain management is particularly complex in the elderly and emergency clinicians should always consider AGS Beers criteria® to avoid inappropriate medications, severe side-effects, and drug-drug interactions. Pain is also a common cause of delirium in older patients. The SARS CoV-2 infection not only can cause acute pain, but also exacerbate chronic pain, particularly in the elderly, who are at high risk to be infected. Looking at all this evidence, emergency clinicians should treat pain with different strategies according to their experience and cultural background, making the right choice for each patient. This work is a critical review of the pain management in the ED, with a particular attention on the

effects of COVID-19 in the EDs. We conducted a systematic search of the following databases: PubMed, Google Scholar, Science Direct, Medline from 2000 to 2020, using the keywords of “pain”, “emergency”, “COVID19”, “elderly”, “palliative care”, “ketamine”, “dexmedetomidine”, and “post-traumatic stress disorder”. The aim of this review is to help emergency clinicians to correctly manage pain in the ED with a new point of view regarding the pain management in COVID-19 patients.

Introduction

Pain management is a common clinical practise in the Emergency Room (ER) being pain a quite frequent cause for referral to the Emergency Department (ED).¹ Even if appropriate pain therapy is a duty for all the emergency medicine physicians in Italy, as reported in the Italian Law 38/2010,² and it is one of the quality-of-care indicators of the ED,³ inadequate treatment of pain is still common in the ED.⁴ Pain management remains a challenge for many critical care physicians⁴ for different causes, as reported by Janati *et al.*,⁵ *i.e.*, the physician’s fear regarding the drug’s side effects, lack of knowledge about opioid dosage, lack of experience in the ED, lack of knowledge about the available pain control medications, and lack of proper supervision by the senior residents. As widely reported in literature,⁶⁻¹⁰ the education process and awareness strategies are crucial in improving the pain management process in the ED. Emergency medicine physicians should always remember that pain is a complex multidimensional condition that affects physical, mental, and social activity of the patients, reducing dramatically their quality of life.^{11,12} As consequence, a multidimensional approach is mandatory to avoid inappropriate pain management, which can result in dysregulation of neuroendocrine system with increased blood pressure and heart rate, and the development of coagulation disorders, pulmonary edema, and heart attack. If not correctly treated and well-managed, acute pain can become chronic, causing severe psychological consequences, such as anxiety, insomnia, depression, and social isolation,¹³ which are common cause for referral to the ER, and of increased costs for the health system.¹⁴⁻¹⁶ Chronic pain is defined as persistent or recurrent pain lasting more than 3 months or beyond the normal tissue healing,¹⁷ with an overall prevalence in the general population of around 20%.¹⁸⁻²⁰ Chronic pain is considered an important public health problem, which can affect any kind of patients and age, but it is more common in elderly patients.¹⁸ It can be a disease *per se*, not a symptom of other diseases.²¹ By definition, chronic pain cannot be treated and managed with a “conventional” therapeutic strategy focused only on the physical aspects of the pain, but a multimodal approach, which pays equal attention to the patient’s psychosocial complaints, is always mandatory in the development of a long-term pain management program.²² In Italy a law to guarantee access to palliative care and pain management has been approved on March 15th, 2020 (Italian Law 38/2010).² This law

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signed a crucial “cultural transformation” in the management of pain based on the dignity and autonomy of the patient in the process of care, and the development of dedicated structures for palliative care. The awareness of this law has been investigated by Del Giorno *et al.* demonstrating that in Italy in 2017, most of the enrolled patients with chronic pain (61.9%) were not aware of the existence of a specific law stating their rights to receive pain management.¹⁸ These results confirm that, despite the Italian Law 38/2010, there was not still adequate awareness about chronic pain in 2017 and unfortunately nowadays in Italy. Del Giorno *et al.* suggested a multilevel approach to solve this problem, bringing together researchers, stakeholders, practitioners, and the general population. Several studies demonstrated that patients whose primary pain is well-managed and treated in the ED have a higher overall satisfaction with hospital services.²³⁻²⁵ As consequence, emergency clinicians should treat pain as soon as possible, avoiding delays while waiting for laboratory or instrumental results. If we focus the attention on acute abdominal pain, pain treatment is an imperative in the ER. Management of acute abdominal pain requires both rapid initial evaluation of pain intensity and early administration of the appropriate analgesic therapy, including patients with a surgical abdomen.²⁶ In the history of the emergency medicine, clinicians used a strategy based on withholding pain medications until a diagnosis has been formulated with the fear that analgesia should alter the physical findings and interfere with diagnosis. In 2021, the delay of acute abdominal pain treatment is no longer acceptable, and emergency medicine physicians must treat pain prior to diagnosis using the most appropriate analgesic drug, as demonstrated by several evidence-based studies.²⁷⁻³⁵ As reported in one 2007 Cochrane review by Manterola *et al.*,³⁶ early administration of analgesia to patients with acute abdominal pain can greatly reduce their pain and does not interfere with a diagnosis, which may even be facilitated due to the severity of physical symptoms being reduced. The same authors reported also that the use of opioid analgesics in the therapeutic diagnosis of patients with acute abdominal pain does not increase the risk of diagnosis error or the risk of error in making decisions regarding treatment.³⁷ In this clinical scenario, a strong-acting opioid, such as morphine, is required, while weak opioids (*e.g.*, tramadol) are not considered adequate first-line agents due to their short duration of effect.^{27,38} Morphine is indicated in the treatment of all types of acute abdominal pain, including acute pancreatitis³⁹ and gallbladder diseases.^{40,41}

When treating a patient with pain in the ED, the primary endpoint is the pain relief by the administration of different systemic analgesic agents according to the pain degree. Emergency medicine physicians should know advantages and disadvantages of choosing and using each drug, and they always should consider the clinical situation of the patients, their age, comorbidities, and medication, avoiding side effects and drug-drug interferences.⁴² Emergency clinicians should treat acute pain with different strategies according to their experience and cultural background, making the right choice for each patient. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used to control acute low-mild degree pain. Their anti-inflammatory effect is due to inhibition of prostaglandin synthesis and thromboxanes by acting on the cyclo-oxygenase enzymes (COX-1, COX-2).⁴³ The inhibition of COX-2 results in a strong anti-inflammatory, analgesic, and anti-pyretic effect, while the selective inhibition of COX-1 increases the risk of bleeding, gastrointestinal tract ulcers and renal dysfunction with acute renal failure.⁴⁴ Ibuprofen is an effective COX-2 non-selective inhibitor that acts rapidly with a good safety profile, including the lowest risk of gastrointestinal bleeding,⁴⁵ and

it can be used also in children.⁴⁶ Ketorolac is a potent non-selective NSAIDs with a rapid analgesic effect (10 minutes) and a half-life about 5-6 hours. Due to its severe gastrointestinal toxicity with an increased risk of bleeding, in Italy, in 2015 the AIFA (Italian Medicines Agency) has forbidden the use of ketorolac combined with other NSAIDs,⁴⁷ and later, in 2017, it has limited the use of ketorolac for the management of moderate-severe post-operative pain (*i.v.* for maximum two days, *per os* for maximum five days) and renal colic.⁴⁸

Paracetamol is considered as NSAID for its analgesic effect even if its mechanism of action is not still completely clear.⁴⁹ Paracetamol is the safest, cheapest, and easy to access drug. It can be used as “opioid-sparing drug” to optimize analgesia and minimize adverse effects, even in the perioperative pain management in children.⁵⁰ Several studies have reported that multimodal regimens of NSAIDs, paracetamol and opioids in appropriate doses, can significantly improve pain scores and reduce narcotic requirements and drug-related side-effects.⁵¹⁻⁵³ Moderate to severe pain usually requires opioid agents: morphine is the most common opioid used in the ED, while fentanyl is mainly used for procedural sedation due to its short half-life.⁵⁴ EMONO (Equimolar Mixture Of Nitrous Oxide and Oxygen) is a safe gas, easy to use, with quick reversibility,⁵⁵ that can be used in painful procedures in the ED, including wound cleaning, burns, sutures, orthopedic procedures, and placement of urinary catheter. EMONO is well-tolerated and a potent analgesic also in children.^{56,57} It generally causes effective and transient analgesia without altering consciousness and cognition. Side effects are generally mild and self-limiting, including nausea, dysphoria, vertigo, and headedness.⁵⁸

Based on the observation that the global demography is changed in the last two decades resulting in an increased number of older people presenting to EDs with greater urgency or with the need to be admitted to hospital,⁵⁹ emergency clinicians should remember that older people’s management can be extraordinarily complex in the ER, and it requires specialist skills and resources.^{60,61} All the physicians should always consider AGS Beers criteria® when they approach the elderly to avoid inappropriate medications, severe side-effects, and drug-drug interactions.^{62,63} Older people can be admitted to the ER for several reasons, including common diseases which are more common with advanced age, *i.e.* hypertension, diabetes mellitus, chronic heart diseases, dementia, and cerebrovascular diseases,⁶⁴ but also acute illnesses that require a faster hospitalization or a longer lengths of stay.⁶⁰ Since their admission in the ER, the emergency physician should be able to clearly identify older patients with frailty at highest risk of poor outcomes and who most likely can benefit from further specialist multidisciplinary interventions.⁶⁵ As reported by Van Oppen *et al.*,⁶⁶ older people wish to have prompt waiting times, efficient care, clear communication, and comfortable environments. They have expectations for holistic care and feel a sense of vulnerability in the ER. Emergency clinicians should always offer adequate assistance to the elderly trying to adapt the principles of geriatric medicine in the ER, and to involve in the discussion around the patients’ need their caregivers, who are a crucial supportive care not only at home, but also in the ER.⁶¹ With the 2019 updates of AGS Beers criteria®, several medications were added to the list of potentially inappropriate medications for most older patients.⁶⁷ In the pain management, tramadol should be avoided for the risk of hyponatremia from syndrome of inappropriate antidiuretic hormone secretion, and opioids should be not prescribed in patients treated with benzodiazepines or gabapentinoids, because the increased risk of severe respiratory depression. If not correctly treated, pain can cause delirium in older patients. Delirium is a geriatric syndrome highly prevalent in hos-

pitalized elderly patients,⁶⁸ particularly in intensive care units⁶⁹ and in patients with dementia.⁷⁰ The diagnosis is clinical. According to the DMS-IV,⁷¹ delirium is a clear disturbance in attention (reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation whether in the environment). The most prominent symptoms are the acute onset of the inability to concentrate and changes in the state of alertness, ranging from agitation to psychomotor stupor. Clinicians must early diagnose delirium due to its high risk of mortality, increased morbidity, and severe distress for the patients.⁷² The acronym “VINDICATE” was created to remember the possible causes of delirium: Vascular, Infections, Nutrition, Drugs, Injury, Cardiac, Autoimmune, Tumours, and Endocrine.⁷³ Delirium is preventable: the most common cause of delirium are drugs, especially those with anticholinergic activity (*e.g.*, diuretics, digitalis, tramadol, benzodiazepines, morphine, codeine, third generation cephalosporins, corticosteroids, tricyclic antidepressants),⁷⁴ and hospitalization. Treatment of delirium is based on non-pharmacological and pharmacological approaches, that should consider the pre-existing clinical diseases of the patient, realizing a mental planning of treatment according to the toxicity of the used drugs.^{75,76} Pain is a well-known cause of delirium, particularly in patients with dementia admitted to hospital;⁷⁷ as consequence, pain treatment can reduce the risk of delirium and is required to manage delirium effectively.⁷⁸ In these patients an effective pain management can contribute to prevent delirium. Pain Assessment in Advanced Dementia (PAINAD scale) is a simple, valid, and reliable instrument for measurement of pain in older patients with cognitive impairment,^{79,80} and it should be used also in the acute setting, including the ED.^{81,82} According to the National Audit of Dementia Care in General Hospitals (Royal College of Psychiatrists, 2017),⁸³ pain and delirium assessments should be routinely conducted and properly recorded for patients with dementia. When treating pain, paraverbal and not verbal communication play a central role in developing empathy for pain,⁸⁴ particularly in elderly patients. Non-pharmacological techniques are easy and simple methods, that can be efficacious in reducing pain and anxiety. Empathy for pain is associated with activity neural networks⁸⁵⁻⁸⁷ and physiological responses, such as skin conductance and increased heart rate.^{88,89} A recent study by Goldstein *et al.*⁹⁰ has demonstrated the positive role of touching on cardio-respiratory function and its analgesic effect via the autonomic nervous system, confirming that social interactions can modify patient’s pain perception,⁹¹ reduce stress and depression.⁹² These findings highlight the analgesic effect of social touch and confirm the importance of social interaction between the patient and the physician or the nurse. In several studies⁹³⁻⁹⁶ music therapy has been demonstrated to reduce anxiety, agitation, and pain, and to have beneficial effects on heart rate, respiratory rate, and blood pressure in the preoperative setting⁹⁷ and in the intensive care unit.⁹⁸ A perspective randomized trial involving patients in the intensive care unit, who require Non-Invasive Ventilation (NIV), has confirmed the beneficial effects of musical intervention in reducing anxiety in critically ill patients and as consequence, to enhance acceptance and tolerance of NIV.⁹⁹ All the findings confirm that the best way to treat pain is always a combined strategy based on pharmacological and not-pharmacological approach. This learning is the basis of an optimal pain management strategy for end-of-life patients in the ED.¹⁰⁰ The scientific knowledge on family caregivers’ experience of pain management in end-of-life care is poor, but the role of family caregivers of patients with cancer or in palliative care is crucial, especially for patients with advanced disease.¹⁰¹ The communication between the emergency clinicians and the family caregivers should be the basis for a correct family caregivers’ engagement in pain management and a good quality patient’s end-

of-life.^{100,102} When possible, the family caregiver should be present in the ER and be an active part of the strategy of pain management. As reported by Smith *et al.*,¹⁰³ emergency clinicians can experience discomfort and distress in treating patients with palliative care needs and find difficult to manage these patients in the ER because of the chaotic environment, the long wait times, and the inability to provide an optimal palliative care in conflict with the wishes of the patients and their family. Eligible patients with signs of an end-of-life trajectory with limited prognoses^{104,105} should be referred to hospice by the emergency clinicians, discussing hospice as a care option with the patient and the family, and working in concert with palliative medicine specialists.¹⁰⁶

The COVID-19 era

The Coronavirus Disease 2019 (COVID-19) pandemic has hardly hit both the global medical community and the worldwide population. Northern Italy has been one of the most seriously affected country and the second, after China, to face such an unexpected pandemic.¹⁰⁷ The spread of the virus has had a deep impact on the Italian healthcare system with the need of a prompt and deep structural and environmental reorganization of the EDs to avoid the collapse of the entire health system.¹⁰⁸⁻¹¹² As consequence, COVID-19 has dramatically and rapidly changed the working routine in the EDs and in all the hospitals with the postponing or cancellation of all elective surgical procedures, outpatient procedures and patient visits, including pain management services.

COVID-19 related acute pain

Considering the overcrowding of the Italian EDs in the so called “phase 1 of the Italian epidemic,” the COVID-19 pandemic has forced the emergency medicine to use all the resources available in the fight against the viral infection and its catastrophic consequences. According to the WHO statistics, the COVID-19 case fatality rate in Italy was considerably higher than in China.¹¹³ COVID-19 is characterized by respiratory symptoms at different degree. Mild infections usually improve within few days, but COVID-19 can cause severe pneumonia with acute respiratory distress syndrome, multiple organ failure and death. As most of the viral infections, pain is quite common also in COVID-19 infected patients, who can differently complain myalgias, arthralgias, abdominal pain and headache.¹¹⁴ As reported in two recent reviews by Widyadharmia *et al.*¹¹⁵ and Alonso-Matielo *et al.*,¹¹⁶ muscle pain or myalgia is one of the most frequent symptoms among COVID-19 infected patients, while neuropathic pain is rarely reported, do not respond well to different therapies, and can be associated with psychiatric disorders, *e.g.*, depression, which can significantly decrease the patient’s quality of life.¹¹⁷ COVID-19 patients can be admitted to the ER for acute abdominal pain,¹¹⁸ or complaining gastrointestinal symptoms, such as vomiting and diarrhea.^{119,120} Headache is a COVID-19 central neurological manifestation reported up to 90.5% of infected patients,^{121,122} which can be associated with fever, anosmia, arthralgia, cough, light headedness, and myalgia¹²² with a mechanism still unknown, but probably due to the release and increase of pro-inflammatory cytokines, the injury to endothelial vessels, and the macrophage and glial activation.^{123,124} COVID-19 has been demonstrated to worsen also chronic pain with several mechanisms, including exacerbation of pre-existing pain, physical or mental complaints, such as stress, anxiety, and depression.^{125,126}

The chronic pain patients

In this dramatic context, the care of chronic pain patients has been significantly impacted with the need to formulate new practise recommendations to inform and help physicians, based on a biopsychosocial model of pain management.^{127,128} As reported in literature, chronic pain patients have higher prevalence of anxiety, depression, catastrophising and suicidal ideation,¹²⁹⁻¹³² and are also at increased risk of COVID-19 due to multiple factors, including comorbidities, old age, and immune suppression.^{133,134} Based on this observation, telehealth and telemedicine with multidisciplinary interactions have been recommended as a safe and effective way to provide medical services and patient education during COVID-19 pandemic. In particular, physicians have been recommended to use telemedicine to evaluate the patient, triage the urgency, and make suitable arrangements for treatment with the main aim to minimise delay and prevent unnecessary visits.

The elderly patients

Considering elderly patients who are generally affected by chronic pain and at high risk to be infected by SARS CoV-2,^{128,135} COVID-19 can significantly impair their quality of life and exacerbate personal disabilities with an increased need of care and underestimated sequelae.

How to treat pain in COVID-19 patients

Adequate analgesia and pain relief is mandatory for all COVID-19 patients. NSAIDs should be avoided to manage fever and pain in COVID-19 patients because evidence suggest that NSAIDs can increase complications from simple respiratory infections or delay recovery from infection based on the assumption that NSAIDs could increase the levels of Angiotensin Converting Enzyme (ACE), involved in the pathogenesis of COVID-19,^{136,137} particularly ibuprofen.¹³⁸ Subsequent observations refuted this assertion.¹³⁹⁻¹⁴¹ When admitted to ICU, COVID-19 patients can develop pain not only for the viral infection, but also for the discomfort associated with ICU treatment, intermittent procedural pain, and chronic pain present before admission to the ICU.¹⁴² If not correctly treated, the combination of pain, prone positioning during mechanical ventilation or extracorporeal membrane oxygenation may trigger delirium and cause peripheral neuropathies, especially when sedation and neuromuscular blocking agents are used.¹²⁸ In the ED prone positioning during Non-Invasive Ventilation (NIV) has been used during COVID-19 pandemic.^{143,144} A continuous infusion of morphine has been used to increase the compliance to NIV (C-PAP in helmet) and reduce the anxiety linked to the situation, which improved the patient's compliance.¹⁴⁵ Ketamine has been suggested by several authors as sedative in mechanically ventilated COVID-19 patients¹⁴⁶ not only for its well-known potent analgesic and sedative effects, but also for its anti-inflammatory role, which could be central in the hyperinflammatory response observed in COVID-19 patients.¹⁴⁷⁻¹⁴⁹ In a case report by Stockton and Kyle-Sidell,¹⁵⁰ dexmedetomidine infusion has been used in a COVID-19 patient with severe hypoxemia treated with High Flow Nasal Cannula (HFNC) with good results in term of oxygenation¹⁵¹ and psychological effects, without the development of severe side-effects. The authors suggest that the pharmacologic properties of dexmedetomidine may help decrease the need for mechanical ventilation in COVID-19 patients and as consequence, patients' mortality. Czepiel *et al.*¹⁵² reported three cases of COVID-19 critically ill patients hospitalized in surge ICUs, who all developed life-threatening hyperpyrexia while being treated with dexmedetomidine for sedation. The authors postulated that the use of high-dose dexmedetomidine (above 1.5 µg/kg/hr) in

a hyperinflammatory state, as COVID-19, can increase the risk of developing hyperpyrexia probably due to the central effects of dexmedetomidine, which can alter hypothalamic temperature regulation through disturbances in neurotransmitter expression and metabolism, and they also recommend using a dose of 0.2–0.7 µg/kg/hr in COVID-19 patients.

The palliative care in end-of-life COVID-19 patients

Palliative sedation in COVID-19 critically ill patients has been a very debated issue during the phase 1 of the pandemic, when the primary endpoint in the EDs and ICUs was the correct distribution of the resources with the main aim to avoid under- and over-treatments. Palliative sedation does not mean euthanasia, but it is the right to die without suffering with a dignified death, even in a so dramatic context as COVID-19 pandemic.¹⁵³ All the emergency clinicians have deeply felt the responsibility of saving many lives as possible, but also the weight of their choices in such a dramatic emergency, particularly for elderly and vulnerable patients.¹⁵⁴ In this difficult situation, emergency clinicians should give best possibilities to those patients who have the highest probability to benefit from intensive care. Alleviation of suffering in critically ill COVID-19 patients is an ethical imperative and a medical duty, and palliative care is the response.^{155,156} As reported by Borasio *et al.*,¹⁵⁷ all dying COVID-19 patients should have access to palliative care, and if possible, emergency clinicians should share every decision-making process with intensivists, avoiding a single person decision, and in presence of refractory pain or worsening of patient's clinical condition, they should share with the patient's family the decision to start continuous palliative sedation based on morphine for pain and dyspnea, midazolam for agitation, haloperidol for delirium, and scopolamine for secretions according to the Italian Law 219/2017.¹⁰⁸

Conclusions

Despite the large number of published manuscripts, pain management is complex and sometimes a challenge in the ED. Emergency clinicians should never underestimate pain and always consider a tailored approach for each patient, particularly COVID-19 patients. The long-term consequences of COVID-19 are still unknown and should be investigated on different levels, *i.e.*, medical and psychological. The future health policies must develop strategies not only to avoid other pandemics, but also and above to encourage immediate and targeted treatment, including palliative care and chronic pain, to reduce serious consequences for the patients and the national health system with a great attention for the EDs and the healthcare workers.

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