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REVIEW

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A comprehensive review of the clinical presentation, diagnosis, and treatment of calcineurin inhibitor-induced pain syndrome

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Abstract

Calcineurin inhibitor-induced pain syndrome (CIPS), a rare but recognized complication of calcineurin inhibitor (CNI) therapy in transplant recipients, presents as severe bilateral lower extremity pain. This syndrome, first described in 1989, primarily affects patients receiving tacrolimus or cyclosporine. Proposed mechanisms include intraosseous vasoconstriction, bone marrow edema, and altered bone metabolism, possibly involving TRSK channels and NFAT signaling. The diagnosis relies on clinical history, characteristic pain patterns, and imaging findings such as bone marrow edema on MRI. The management of CIPS revolves around reducing or discontinuing the offending CNI while maintaining immunosuppression. Alternative immunosuppressants like mammalian target rapamycin (mTOR) inhibitors or mycophenolate mofetil are considered to mitigate symptoms. Symptomatic relief includes calcium channel blockers, bisphosphonates, and analgesics like NSAIDs or opioids. Physical therapy and close monitoring are also integral to improving outcomes and managing chronic pain effectively in affected transplant recipients. This review synthesizes current knowledge on CIPS, highlighting diagnostic challenges, treatment options, and areas for future research to optimize clinical management and enhance patient outcomes.

Keywords Calcineurin inhibitor-induced pain syndrome, Calcineurin inhibitors, Diagnosis, Treatment

Introduction

Calcineurin inhibitor-induced pain syndrome (CIPS), also known as the "symmetrical bone syndrome," is a condition characterized by reversible lower extremity pain in organ transplant patients receiving calcineurin inhibitors, particularly tacrolimus and cyclosporine [1]. First described in 1989 by Bouteiller et al. in patients treated with cyclosporine, the term CIPS was introduced in 2001 by Grotz et al., who identified tacrolimus as a contributing factor [2, 3]. Calcineurin is a serine/threonine phosphatase enzyme found in all mammalian tissues, particularly in the central nervous system [4–6]. It regulates various physiological processes, including enzymatic and ion channel functions, membrane

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vesicle activities, cardiac and bone development, immune response, and blood vessel tone [3, 6]. Calcineurin activates the immune system by binding to the nuclear factor of activated T cells (NFAT), essential for immune function [6]. Immunosuppressive drugs like cyclosporin A and tacrolimus (FK506) target calcineurin to prevent organ transplant rejection but can cause diverse adverse effects; such as CIPS [7].

The prevalence of CIPS varies, with estimates ranging from 1 to 17% of patients with solid organ or hematopoietic stem cell transplants, as well as those using CNIs for inflammatory conditions like Crohn's disease [1, 8, 9]. This suggests that CNIs themselves are a critical etiologic factor for CIPS, not the clinical setting. Topical CNI use does not cause CIPS, indicating systemic exposure is necessary [9].

Clinically, CIPS manifests as symmetrical bilateral pain in the lower extremities, particularly in the feet, ankles, and knees, which is usually dull but can also feel like electric shocks; some cases involving back pain have been reported [9, 10]. The pain often worsens with movement or resting legs below heart level and has no clear correlation with calcineurin inhibitor blood levels, making the timing of symptom onset unpredictable [7, 9, 11–13]. The pain is severe and prevents patients from working or performing their normal daily activities; some patients cannot walk when they have symptoms in their lower extremities [10, 14]. Cutaneous tactile allodynia and hyperalgesia are also reported [12, 15]. Symptoms vary in severity and onset, occurring 3–18 months after CNI exposure, and can take up to 18 months to resolve, with some cases recurring [3, 15–17].

The exact pathophysiology of CIPS is unknown. It has been proposed that it involves CNI-induced intraosseous vasoconstriction, leading to hypoperfusion, bone marrow edema, and bone compartment syndrome [3, 18]. Another hypothesis is that CNI affects nociceptive processes by activating the nitric oxide pathway, interfering with the cation channels of nociceptive sensory neurons, and through gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptor modulation [4, 7, 19, 20].

Diagnosis is by exclusion, which means other more common causes of musculoskeletal, neuropathic, and ischemic pain must be ruled out. It is often based on clinical suspicion, but radiologic criteria have been proposed. Imaging of the affected areas presents normal plain radiographs, bone scintigraphy will show increased tracer uptake in the affected bones and joints (Fig. 1) and MRI shows patchy edema of the bone marrow [10, 11, 13, 21]. Blood CNI concentration can be elevated or within the normal range; interestingly, elevated alkaline phosphatase is a common lab finding [10, 16].

The treatment for CIPS remains challenging and mainly focuses on symptom management and reducing the CNI concentration to the normal therapeutic range, as the underlying mechanisms driving the syndrome are not fully understood. Despite its rarity, CIPS significantly impacts patients' quality of life, highlighting the need for further research into its prevention and treatment strategies.

The objective of this article is to provide a comprehensive review of CCIPS focusing on clinical presentation, diagnosis, and treatment strategies. Moreover, this manuscript explores the pathophysiology underlying CIPS, discusses diagnostic criteria and challenges, evaluates current treatment approaches, and addresses prognosis and long-term outcomes. By summarizing key findings and identifying areas for further research, this narrative review aims to enhance understanding and improve clinical management of CIPS for better patient outcomes.

Methodology

This narrative review undertakes a comprehensive assessment of CIPS, focusing on current understanding and management strategies. The inclusion criteria limited consideration to full-text articles published in English between 2000 and 2024. This timeframe was chosen to encompass established practices and capture significant advancements. Extensive electronic searches were conducted across PubMed, EMBASE, Google Scholar, and Scopus using key terms such as "Calcineurin Inhibitor Induced Pain Syndrome," "CIPS," "CNIs and pain," and related variants (Table 1).

To supplement electronic searches, manual searches were performed on references cited in relevant reviews and included articles. Additionally, exclusion criteria excluded abstracts, letters, editorials, posters, and unpublished or non-peer-reviewed studies to ensure the inclusion of only high-quality, reliable evidence. The review did not impose a predetermined limit on the number of studies included, aiming for a comprehensive synthesis of knowledge on CIPS across various study designs including descriptive and analytic studies. Moreover, both preclinical and clinical investigations were considered to provide a broad perspective on CIPS, covering aspects such as pathophysiology, clinical presentation, diagnostic approaches, and therapeutic interventions. Table 1 outlines a summary of the methodology employed.

Pathophysiology of CIPS

Overview of CNI and their mechanisms of action

Calcineurin is a calmodulin-activated serine phosphatase that participates in multiple cellular processes and is essential for calcium-dependent signal transduction pathways [22, 23]. It plays a crucial role

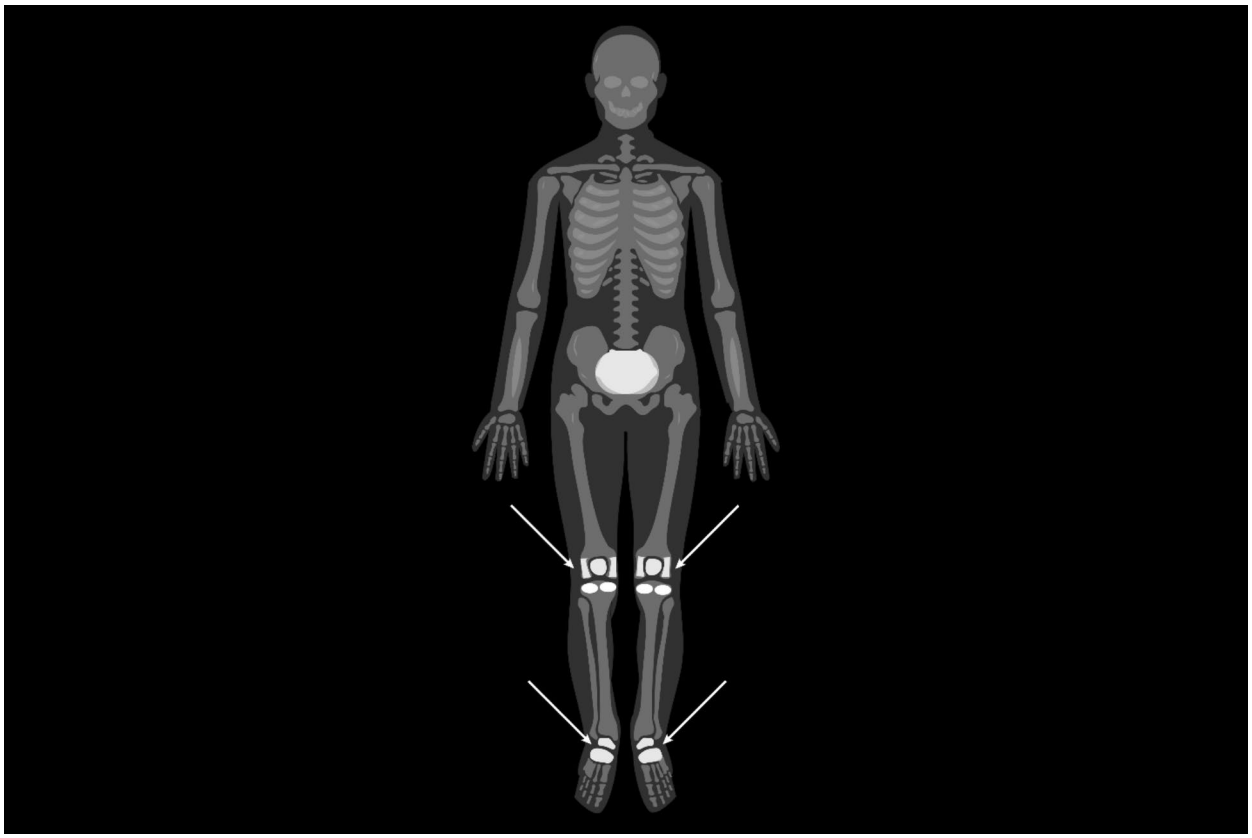

Fig. 1 Bone scintigraphy showing increased uptake in affected bones and joints in CIPS

Table 1 Methodological summary

Methodology steps	Description
Literature search	PubMed, EMBASE, Google Scholar, and Scopus were thoroughly searched to gather relevant literature on CIPS
Inclusion criteria	Articles were required to be written entirely in English, include both adult and pediatric populations, cover research conducted in both pre-clinical and clinical settings, and emphasize drug-induced conditions
Exclusion criteria	Studies that had not been published or undergone peer review, presentations in poster format, conference or standalone abstracts, letters, and editorials were excluded from consideration
Search terms	Key search terms included "Calcineurin Inhibitor Induced Pain Syndrome," "CIPS," "CNIs and pain," and related variants, coupled with indicators such as "immunosuppressive therapy and pain"
Additional search	References cited in recent reviews focused on specific diseases were manually inspected for additional sources. No predefined limit was set on the quantity of studies considered. Studies encompassed descriptive studies, cohort studies, and observational studies

in neurological development, immune response, and tissue remodeling and also works as a nociceptor modulator [19, 23]. Comprised of two subunits, the catalytic calmodulin-binding subunit (calcineurin-A) and the calcium-binding regulatory subunit (calcineurin B), it is activated upon the interaction of naive T cells with an antigen-presenting cell, resulting in the release of interleukin 2 and T cell activation [1, 22–25]. Due to its involvement in immune system activation, drugs have been developed to inhibit calcineurin, thus suppressing the production of proinflammatory cytokines. Calcineurin inhibitors are considered the first-line therapy for immunosuppression in transplant patients, with cyclosporine and tacrolimus being the main drugs [24, 26]. They act as prodrugs, binding to specific receptors in the cytoplasm, known as immunophilins, to regulate calcineurin activity. Cyclosporine binds with cyclophilins and tacrolimus with FKBP12 [22, 24, 26]. Calcineurin inhibitors competitively antagonize calcineurin [23]. When bound to

receptors, they prevent dephosphorylation and activation of factors dependent on calcineurin, such as the transcription factor nuclear factor of activated and T cells inhibiting the activation of IL-2, IL-4, and CD40 and T cells amongst others [19, 22, 23, 26].

Proposed mechanisms underlying the development of CIPS

The pathophysiology of CIPS remains unknown, yet several potential mechanisms have been proposed [1, 3]. First, it is important to know that calcineurin can work as a nociceptor regulator, hence changes in this protein could change the pain threshold and also lead to a different perception of pain in humans [19]. The studies have found that CNIs induce alterations in vascular permeability leading to altered bone perfusion and permeability. This leads to intraosseous vasoconstriction and bone marrow edema that could explain the pain [1, 27]. Other studies have proposed that these drugs can change bone metabolism and cause pain because of decreased osteoblastogenesis and an increase in bone turnover [25, 28]. Furthermore, some studies suggest that CIPS could be caused by an impaired modulation of the TRSK current, by increasing neural excitability and ultimately enhancing pain sensitivity [29].

Role of calcineurin signaling pathway in pain modulation

Calcineurin acts as a nociceptor modulator by helping to maintain a normal baseline of physiologic sensory neural and glial functions by regulating potassium currents and resting membrane potential. This is done by different pain pathways, like the potassium channel TRESK, the NFAT, and the AMPA receptors [19, 29–31]. The TRESK protein is a two-pore potassium channel that is involved in pain sensitivity. Calcineurin regulates the TRESK by dephosphorylating specific serine residues. The interaction of calcineurin and TRESK contributes to the development of pain by regulating the excitability of sensory neurons and nociceptors (Fig. 2) [19, 29, 32].

Apart from the TRESK pathway, there is the NFAT pathway, one activated by high concentrations of calcium. In non-activated cells, NFAT is phosphorylated and is only present in the cytoplasm (Fig. 3). Once calcium increases, NFAT is dephosphorylated by calcineurin, which causes it to be translocated to the nucleus and leads to the transcription of pronociceptive genes and to an overexpression of pronociceptive chemokine receptors in the dorsal root ganglion, which contributes to pain perception [19, 24, 33].

There are also AMPA receptors, which are tetrameric proteins composed of four subunits [34]. Glutamate binds to these receptors by opening its channels allowing positively charged ions such as calcium and sodium to pass through. The postsynaptic depolarization caused

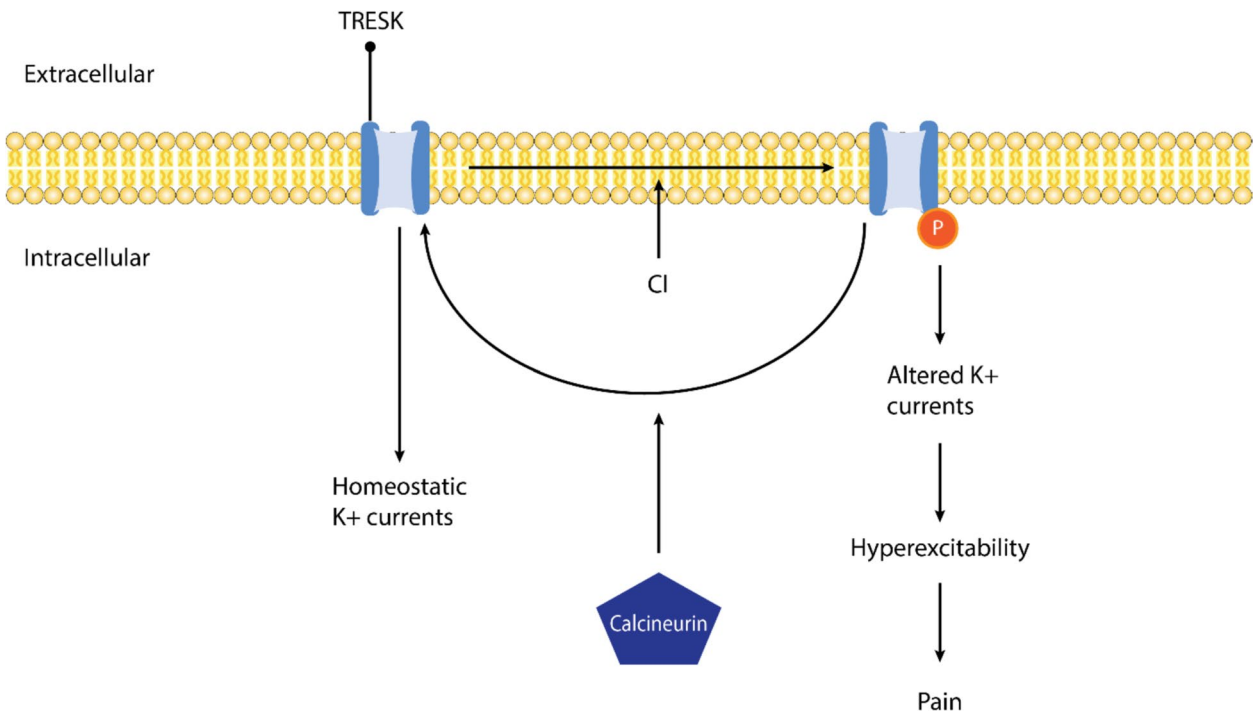

Fig. 2 Potential mechanisms of calcineurin inhibitor-induced pain

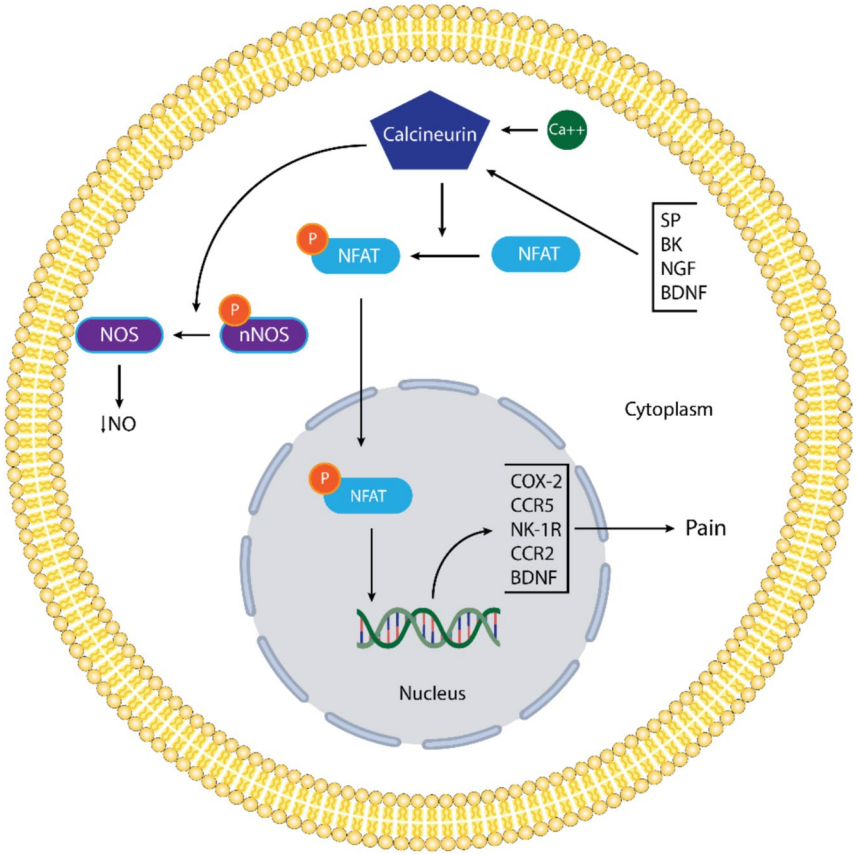

Fig. 3 Potential mechanism of calcineurin in pain regulation

by these receptors is essential for the transmission of pain signals. Calcineurin regulates calcium-permeable AMPA receptors on parasympathetic neurons in the hypothalamus via the GluA1/GluA2 pool mediated by α2δ−1 [31, 35].

Interaction between calcineurin inhibitors and pain pathways

CNIs interact with different pain pathways in different ways, but in most cases, they have similar results. CNIs prevent the dephosphorylation of NFAT, which prevents the expression of certain pronociceptive genes and the activation of proinflammatory interleukins that help regulate pain perception. Calcineurin inhibition increases interactions between α2δ−1 and synaptic NMDA receptors by tonically activating these receptors in the spinal cord, leading to pain hypersensitivity [4]. Studies have shown that tacrolimus induces hyperexpression and synaptic hyperphosphorylation in one of the GLuA1 subunits of AMPA receptors in the dorsal horn of the spinal cord through the inhibition of calcineurin. Upregulation of AMPA receptors and inhibition of calcineurin contribute to pain development by improving excitatory neurotransmission and action potential speed in nociceptive pathways [36]. Furthermore, it is believed that the calcineurin inhibitor cyclosporine can attenuate the antinociceptive effects of morphine via the activation of the nitric oxide pathway by dephosphorylation of the neuronal nitric oxide synthase and reducing its activity [19].

Clinical presentation of CIPS

Common symptoms and manifestations of CIPS

A primary feature of CIPS is the presence of severe, deep-aching pain, primarily localized to the lower extremities of the body. The pain typically presents as bilateral with a symmetrical distribution localized towards the feet, ankles, knees, and occasionally the forefeet [3]. It is hypothesized that pain is localized to the lower extremities because that is the site of greatest venous blood pressure [37]. It is also worth noting that while most patients describe the pain as a deep-aching sensation, there are other accounts of the pain resembling an electric shock or a sense of tingling, indicating a degree of variability in symptom manifestation [37]. Lavoratore et al. (2009) highlighted the severity of the pain that can present in

CIPS [37]. It has been noted in many different case studies that the pain can be to such a debilitating degree that many patients will necessitate the use of crutches or even wheelchairs [3, 9, 10, 38]. The discomfort linked with CIPS typically starts several months following the commencement of immunosuppressive treatment and is exacerbated by walking and weight-bearing tasks but can be alleviated by encouraging the patient to elevate their legs [37]. The pain is refractory to normal analgesics and significantly affects patients' quality of life and functional capabilities. This impairment in mobility was additionally emphasized by Ullah et al. (2021) who noted that "the relentless pain affected mobility to the extent that some patients became wheelchair dependent" [9].

Variability in symptom presentation among individuals

The clinical presentation of CIPS is significantly variable, especially in terms of symptom severity and onset. CIPS can manifest shortly after the initiation of CNI therapy, even within a few hours, and this is what would be considered an acute onset [37]. Alternatively, it could take several months of CNI therapy for symptoms to appear, in which case we'd have a chronic onset. Lavoratore et al. (2009) documented cases where symptoms appeared "as soon as 12 h after the first dose of calcineurin inhibitor, while others experience pain onset 14 months after initiating therapy" [37]. This variability highlights the necessity of close monitoring of patients undergoing CNI therapy. Moreover, although most patients experience the alleviation of symptoms when they cease or decrease their dosage of CNIs [3], a subset of patients may persistently endure chronic pain if there is a delay in the diagnosis or if CNI treatment is sustained at elevated levels.

The intensity of symptoms can greatly differ from person to person. Certain individuals experience minor discomfort that can be controlled through dosage modification [37], whereas others may endure severe pain that hinders their everyday activities [3]. Ullah et al. report that "the severity of symptoms varies, but significant disability is often observed, including cases where patients became wheelchair dependent" [9]. Additionally, the nature of pain can differ, with most patients describing it as dull and persistent, while a few cases have reported sharp, electric shock-like sensations [37]. Atypical manifestations have been documented, with reports of pain spreading to regions typically unaffected by CIPS, such as the spine and the upper extremities [9]. Lavoratore et al. (2009) brought attention to a particular case featuring "high signal intensity in the periosteal regions of femora and tibiae, a finding not commonly reported in the literature" [37]. These unusual presentations may introduce challenges in diagnosing the condition and hinder the administration of a suitable therapy.

Interestingly, certain patients may demonstrate partial or complete alleviation of symptoms upon changing from one CNI to another, although this effect is not universally successful [37]. Collini et al. (2006) [38] observed that "pain disappeared within a timeframe of 3 to 18 months from the onset of symptoms following a reduction in the dosage of immunosuppressive treatment." Nonetheless, in a few cases, symptoms persisted despite the switch in CNIs, indicating that individual responses to different CNI medications can exhibit considerable diversity [37]. Genetic variations play a significant role in the variety of symptom manifestations. Polymorphisms in enzymes and transporters involved in drug metabolism, like CYP3A4, CYP3A5, and ABCB1 [39], can impact the metabolism of CNIs and influence the susceptibility and severity of CIPS. Tedesco et al. (2012) [39] elaborate on the significance of these genetic elements, noting that individuals who have the CYP3A5*3 allele may require lower CNI doses to reach therapeutic levels.

Potential risk factors associated with CIPS

Identification of risk factors for CIPS is essential for effective prevention and treatment. Various risk factors have been identified that could increase the likelihood of individuals developing CIPS. The administration of high doses of CNIs is one of the most notable risk factors [3]. When the blood levels of CNIs are elevated, there is a strong positive correlation with the development of CIPS. This is because the neurotoxic effects of CNIs become more prominent at higher concentrations [39]. Ullah et al. (2021) noted that "patients receiving high-dose cyclosporine were significantly more likely to develop CIPS, underscoring the dose-dependent nature of this syndrome" [9]. Additionally, rapid dose escalation can trigger CIPS by overwhelming the body's adaptive mechanisms [8]. The length of CNI treatment plays a role in the likelihood of developing CIPS. Individuals who undergo extended periods of immunosuppressive therapies face a higher risk, as prolonged use of CNIs can worsen vascular issues and disrupt bone metabolism. This is especially noticeable in patients who have had multiple transplants or undergone intense chemotherapy, as the cumulative effect increases the risk as noted by Lavoratore et al. (2009) [37]. The potential risk associated with CIPS is amplified when CNIs are administered at high dosages and titrated rapidly, especially in the initial stages of treatment [3]. Grotz et al. (2001) suggest that "a slow and steady approach to CNI dosing, with frequent monitoring, is essential to mitigate the risk of developing CIPS. Rapid increases in drug levels can precipitate the onset of symptoms due to sudden changes in vascular and neuronal dynamics" [3].

Patients who have undergone a previous solid organ or hematopoietic stem cell transplantation are more susceptible to developing CIPS in the future and upon return to CNI therapy [9]. The cumulative exposure to CNIs and the aggressive immunosuppressive regimens used in these patients contribute to developing CIPS. Ullah et al. (2021) highlight that "patients with a history of multiple transplants and those who received high-dose myeloablative conditioning regimens showed a higher propensity for developing CIPS" [9]. The same goes for individuals with a history of CIPS as they are more susceptible to a relapse when re-exposed to CNIs. Lavoratore et al. (2009) documented instances in which "patients developed CIPS only following the 2nd hematopoietic stem cell transplantation, indicating a cumulative risk associated with repeated CNI exposure" [37]. Various forms of organ transplants, including kidney and heart transplants, seem to have a higher likelihood of being linked to CIPS. According to Collini et al. (2006), "About 5% of patients undergoing kidney, heart, lung, liver pancreas, or bone marrow transplantation were affected by CIPS" [38]. Kidney and heart recipients were noted as being particularly susceptible to CIPS. The patients who have concurrent medical conditions that hinder vascular health or bone metabolism, such as diabetes, hypertension, and vascular diseases, may also face an elevated risk of developing CIPS. These conditions have the potential to intensify the vasoconstrictive impacts of CNIs, thereby increasing the vulnerability to bone marrow edema and pain. According to Prommer et al. (2012), "Patients with compromised vascular function are more likely to experience the vascular disturbances induced by CNIs, which are central to the pathophysiology of CIPS" [6].

CIPS can impact individuals across all age groups, but it is frequently seen in younger patients such as children and adolescents. Their increased vulnerability may be attributed to the differences in drug metabolism and pharmacodynamics of younger patients as opposed to adults [40]. Furthermore, some research has suggested a greater occurrence of CIPS in females, which is possibly associated with the increased hormonal effects on pain sensitivity and drug metabolism [40]. Genetic variations in drug transporters and metabolizing enzymes are significant factors contributing to the difference in CIPS risk among individuals [39]. Tedesco et al. (2012) explain that "polymorphisms in the ABCB1 gene, which encodes a drug transporter protein, and the CYP3A5 gene, involved in CNI metabolism, significantly affect the pharmacokinetics of these drugs, thereby influencing the risk of developing CIPS" [39]. Patients diagnosed with autoimmune disorders, such as lupus nephritis or inflammatory bowel disease, who undergo treatment with CNIs, are also susceptible to developing CIPS [41]. The immunosuppressive effects of CNIs in these conditions can worsen the risk of developing this pain syndrome. Safarini et al. (2024) noted that "the use of CNIs managing autoimmune disease has been associated with CIPS, suggesting that these conditions might predispose patients to the syndrome" [41]. Furthermore, the simultaneous administration of additional neurotoxic medications can significantly enhance the likelihood of CIPS. Specific antibiotics and chemotherapeutic agents have the potential to worsen the neurotoxic consequences of CNIs. Lavoratore et al. (2009) highlighted that "patients on multiple neurotoxic drugs exhibited a higher incidence of CIPS, indicating a compounded risk from drug interaction" [37] (Table 2).

Diagnosis of CIPS

Diagnostic criteria and guidelines for CIPS

Diagnosis of CIPS is essentially predicated based on its unique clinical presentation and radiological findings. As outlined before, patients typically present with severe, symmetrical, and debilitating pain, primarily in the lower extremities. This pain is often exacerbated by weight-bearing activities and may also present with features such as hyperalgesia (increased sensitivity to pain) and allodynia (pain due to stimuli that do not usually provoke pain) [12].

Most of the time, laboratory tests show no changes, which may discard other pathologies related to inflammation or rheumatological processes [38]. In fact, calcineurin-inhibitor serum concentrations might remain within normal parameters. However, some cases report an elevation in alkaline phosphatase and serum calcium levels, although this increase is not consistent in all cases reported [9, 42, 43]. Due to these differing opinions, there is a dearth of set guidelines for the treatment of this condition.

Radiological findings play a chief role in diagnosing CIPs, with MRI being the most sensitive diagnostic tool. It shows low T1 and high T2 signals that correlate with bone marrow edema in the affected subcondylar and periarticular bone, however, these findings can also be consistent with osteonecrosis, osteoporosis, or ischemia [11, 44]. Signal changes in T1 and T2 signal changes show increased vascularization, metabolism, and perfusion, which explain the vascular compromise that leads to edema and increased bone turnover [38, 45]. Bone scintigraphy shows a bilaterally increased tracer uptake in joint and bone which affect most commonly the knees and feet, nonetheless, there are no differences in radiographies [9, 11, 38, 46]. Some cases of CIPS have shown X-ray findings related to osteoporosis and osteopenia [11, 44].

Table 2 Checklist for clinical presentation and diagnosis of CIPS

Checklist for clinical presentation and diagnosis of CIPS
- [] Identify the primary drugs associated with CIPS: cyclosporine and tacrolimus
- [] Recognize CIPS as a drug-induced pain disorder
- [] Note the typical presentation: intense, bilateral pain localized to the lower extremities
- [] Understand the pain onset timeframe: 3–14 months post-transplant
- [] Recognize other common symptoms: symmetrical pain in feet, ankles, knees
- [] Note the impact on quality of life and functional capabilities
- [] Identify CIPS as a reversible condition with dosage adjustment or cessation of CNIs
- [] Recognize variability in pain sensation: deep-aching, electric shock, tingling
- [] Note the significant impairment in mobility: use of crutches or wheelchairs
- [] Understand the timing of symptom onset post-commencement of immunosuppressive treatment
- [] Recognize the refractory nature of pain to normal analgesics
- [] Acknowledge the importance of differential diagnosis: polyneuropathy, osteoporosis, hyperparathyroidism
- [] Identify key diagnostic imaging findings: normal radiographs, increased tracer uptake on bone scintigraphy, MRI showing bone marrow edema
- [] Recognize the importance of differentiating CIPS from conditions with varying treatment modalities
- [] Note laboratory abnormalities: elevated alkaline phosphatase, normal inflammatory markers
- [] Recognize acute vs. chronic onset of symptoms
- [] Note the potential for alleviation of symptoms with cessation or reduction of CNIs
- [] Recognize partial or complete alleviation of symptoms with switching CNIs
- [] Understand the role of genetic variations in symptom manifestation
- [] Identify high doses of CNIs as a significant risk factor
- [] Recognize the impact of rapid dose escalation on CIPS development
- [] Understand the cumulative risk with repeated CNI exposure and multiple transplants
- [] Acknowledge the susceptibility in patients with concurrent medical conditions: diabetes, hypertension, vascular diseases
- [] Identify younger patients, especially children and adolescents, as more vulnerable
- [] Note the genetic factors influencing CIPS risk: polymorphisms in drug transporters and metabolizing enzymes
- [] Identify the increased risk in patients with autoimmune disorders undergoing CNI treatment
- [] Recognize the compounded risk from concurrent neurotoxic medications

Differential diagnosis and exclusion of other conditions

Differential diagnosis is a critical aspect in the assessment of CIPS, given its potential overlap with various disorders including musculoskeletal and neuropathic pain disorders. Osteonecrosis is a differential diagnosis that usually presents as hip pain without involving knees or ankles. MRI shows bone marrow edema, however, on T2 sequence a double line sign typical of this pathology is shown [11, 44]. Another differential diagnosis is osteoporosis, which involves hip or spine pain, however, it is common to find it in patients with CIPS [38, 44]. Musculoskeletal pain differential diagnosis includes insufficiency fracture, gout, and secondary hyperparathyroidism among other pathologies [11].

Although some patients with CIPS have referred pruritus, it may exclude rheumatological pathologies with the absence of skin changes, limited movement, and swelling, among other clinical manifestations of this disease [11]. Additionally, laboratory investigations might indicate heightened alkaline phosphatase levels in CIPS patients, although inflammatory markers and other rheumatological parameters typically stay within normal ranges [38]. Reflex sympathetic dystrophy syndrome (RSDS) is another differential diagnosis that involves intense pain in the hands, knees, and feet, but unlike CIPS, its pattern is asymmetric. Moreover, the temperature of the skin increases with color changes. Moreover, there are vasomotor instability signs and edema in the extremities [11, 12, 38, 47]. Differential diagnoses of low bilateral pain include polyneuropathy, avascular necrosis, myositis, complex regional pain syndrome, lumbar spinal canal stenosis, or disc hernia [12, 43, 47].

Challenges and limitations in diagnosing CIPS

CIPS is an underdiagnosed condition due to the limited descriptions. CIPS diagnosis represents a challenge due to the lack of well-established criteria and nonspecific laboratory test changes. Also, clinical manifestations intertwined with several differential diagnoses such as osteoporosis, osteonecrosis, and RSDR [7]. Future studies

should incorporate laboratory test comparison before, during, and after the use of the calcineurin-inhibitors, to analyze calcineurin-inhibitor range concentrations and other laboratory variations such as alkaline phosphatase or calcium. A study made in 1998 showed that the use of L-type Ca2 + channel blockers used to treat hypertension caused by calcineurin inhibitors could camouflage CIPS by regulating the spinal dorsal horn glutamate entrance [7].

On the other hand, there is a study that hypothesizes CIPS is an early manifestation of HHV6-associated encephalitis/myelitis, which is localized in the dorsal horn of the spinal cord, future studies should analyze the dorsal horn role in the CIPS as well as other immunosuppressive factors that might trigger this pathology [43].

Treatment approaches for CIPS

CIPS currently lacks specific therapeutic protocols, making its management particularly challenging. The primary treatment recommendations involve discontinuing, reducing the dose, or switching to another CNI (Fig. 4) [3, 7, 46, 48]. However, in cases of allogeneic stem cell transplantation, these strategies risk exacerbating graft-versus-host disease (GVHD), due to the resultant decreased CNI concentrations [17, 42]. The absence of prospective or randomized controlled trials further complicates the definition of effective therapy for CIPS. The largest available studies are case series, which similarly endorse adjusting CNI regimens [10, 13, 17, 38, 42, 47, 49]. Given the limited evidence, the current management of CIPS is largely based on expert opinions and focuses

Fig. 4 Comprehensive Treatment Protocol for Calcineurin Inhibitor Induced Pain Syndrome (CIPS)

on symptomatic relief, with the possibility of spontaneous remission.

Conservative management strategies for CIPS

Conservative management of CIPS focuses on adjusting the immunosuppressive regimen. Suggested approaches include reducing the doses of CNI or switching to a different CNI [10, 13, 17, 38, 42, 47, 49]. If dose reduction or CNI switching is ineffective, discontinuation of the CNI or switching to alternative non-calcineurin agents, such as the mechanistic target of rapamycin (mTOR) inhibitors, has been recommended [17, 50–52]. While these strategies can be effective, they also carry the risk of exacerbating GVHD due to reduced CNI concentrations [17, 42]. It is essential to carefully balance these adjustments with the potential risk of worsening GVHD and consider that switching to another CNI may be preferable when GVHD is not fully resolved or shortly after remission [17]. It is important to consider that although some cases of CIPS resolve spontaneously, most show improvement through dose reduction or withdrawal of CNIs [9, 10]. However, certain cases may be refractory to conservative management [46].

Pharmacological Interventions for CIPS

Pharmacological management of CIPS has shown varied success with different classes of drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally ineffective and should be avoided due to the risk of nephrotoxicity [9, 53]. Simple analgesics and opioids also do not provide adequate relief for CIPS [9, 17]. However, gabapentinoids such as gabapentin and pregabalin, commonly used for neuropathic pain, appear promising due to their mechanism of action involving the binding to the alpha-2/delta-1 subunits of voltage-gated calcium channels [1, 50, 53, 54]. Case reports have documented significant pain relief with pregabalin, particularly at doses of 75 mg to 150 mg twice daily, suggesting its potential effectiveness in treating CIPS [53].

Calcium channel blockers (CCBs) have shown mixed results in managing CIPS. While earlier studies indicated potential benefits with dihydropyridine derivatives such as nifedipine and amlodipine, recent evidence has questioned their effectiveness [10, 11, 14, 16, 37, 42, 48]. Nonetheless, some patients have experienced improvement when switching calcineurin inhibitors and starting CCB treatment [1].

Other pharmacological options include bisphosphonates like pamidronate and clodronate, which can alleviate pain by inhibiting osteolysis [8]. Calcitonin has also been used to manage CIPS [9]. Intrathecal N-methyl-D-aspartate receptor (NMDAR) antagonists, such as AP5, and systemic administration of memantine, a clinically available NMDAR antagonist, have shown potential in animal models for reversing mechanical hypersensitivity and reducing allodynia and hyperalgesia-induced by calcineurin inhibitors [7]. These findings suggest that NMDAR antagonists could be a future avenue for treating CIPS in clinical settings.

Overall, while several pharmacological interventions show promise, the effectiveness of these treatments often depends on individual patient responses and should be considered in conjunction with adjustments to the immunosuppressive regimen.

Non-pharmacological interventions for CIPS pain

Non-pharmacological interventions for CIPS have not been widely documented, and there are no specific reports on the effectiveness of physical therapy, exercise, or transcutaneous electrical nerve stimulation (TENS) in treating CIPS pain. However, given that CIPS shares strikingly similar mechanisms with neuropathic pain, further research into these modalities is warranted [4, 20]. In cases of neuropathic pain, TENS has been used to improve symptoms, though its efficacy remains controversial [55]. Investigating the utility of TENS in CIPS could provide new avenues for symptom management.

Currently, the only documented non-pharmacological approach for CIPS involves recommendations for rest and leg elevation, which have been shown to offer symptom relief [9, 38, 53]. However, the patients in these reports also received adjustments in CNI or other pharmacological interventions. Therefore, the true utility of rest and leg elevation alone cannot be determined. Moreover, in a therapeutic trial involving two patients, hyperbaric oxygen therapy was used to treat CIPS but showed no positive effects [16]. Further studies and clinical trials are needed to explore the broader scope of non-pharmacological treatments for CIPS to enhance patient care and quality of life.

Future directions

Looking ahead, it is imperative to establish a more standardized management pathway for patients suffering from CIPS. Although spontaneous remission is frequent, the severe impact of CIPS on the quality of life and the resultant inability to carry out daily activities during its presence underscores the need for ongoing research. Developing a comprehensive and evidence-based treatment protocol will help improve patient outcomes and provide clear guidance for healthcare providers in managing this challenging condition. Continued investigation into both pharmacological and non-pharmacological interventions will be crucial in enhancing our understanding and treatment of CIPS, ultimately aiming to

alleviate the significant burden it places on affected individuals.

Prognosis and long-term outcomes

Natural course of CIPS

CIPS typically follows a self-limiting natural course. As evidenced in the literature, the onset of severe musculoskeletal pain usually occurs within the first 6 months after initiating CNI therapy for kidney transplantation, with a mean onset between 3 and 6 months in most cohorts studied. The pain is characteristically severe and disabling, often preventing patients from normal activities like ambulation [10]. However, a key feature of CIPS is the tendency for spontaneous resolution of symptoms over time, even if CNI therapy is continued unchanged. Across the reviewed studies, most patients became completely asymptomatic within 3–9 months after the initial pain onset. Long-term follow-ups ranging from 9 months to over 4 years showed patients remained pain-free with no residual musculoskeletal abnormalities related to their prior CIPS episode [10].

Factors influencing prognosis and treatment response

While the natural history is generally favorable, certain factors may influence the prognosis and response to treatment in CIPS. Elevated CNI trough levels at pain onset were reported in some but not all cohorts, suggesting high CNI exposure may contribute to syndrome development but are not always requisite. Prompt recognition and supportive management avoiding potentially aggravating factors like weight-bearing appear prudent during the acute phase based on anecdotal reports [10].

Pharmacologic interventions have shown mixed results. In some earlier cases, CCBs provided pain relief but were ineffective in a more recent larger series. Conversely, the newer agent pregabalin has shown promise in alleviating CIPS symptoms while allowing continuation of CNI therapy. Reducing CNI dosing to lower trough levels in the therapeutic range is also a reasonable approach when feasible [10].

Emerging evidence suggests that the cumulative exposure and dosing of calcineurin inhibitors, particularly tacrolimus, may be an important determinant of CIPS prognosis and treatment response. A study found a positive correlation between higher cumulative tacrolimus doses at 12 and 24 months post-transplant and the development of CIPS. Moreover, in the four CIPS cases identified, complete withdrawal of tacrolimus was required to achieve pain relief, pointing to discontinuation of the offending calcineurin inhibitor as a potential management strategy. Interestingly, patient factors like age, severity of underlying liver disease, biochemical parameters, and use of concomitant steroids like methylprednisolone did not appear to impact CIPS risk or outcomes. However, the small number of CIPS cases limits the ability to draw definitive conclusions about prognostic variables and optimal therapeutic approaches. Nonetheless, these findings underscore the likely importance of minimizing cumulative calcineurin inhibitor exposure, possibly through dose minimization or alternative immunosuppression regimens, in influencing the natural course and treatment responsiveness of this syndrome [44].

Impact of CIPS on patient quality of life and daily functioning

The case reports vividly illustrate how CIPS is far more than a mere nuisance pain. The intense abdominal pain, nausea, vomiting, watery diarrhea (at times bloody), and weight loss inflicted by CIPS can severely undermine a patient's nutritional status, energy levels, and ability to carry out basic daily activities [51]. Patients have described periods of "prostration", a state of profound weakness and exhaustion leaving them largely bedridden.

Perhaps most insidious is the severe deep muscle and bone pain that can render patients almost completely immobilized. One case documented a patient who, due to crippling bilateral lower extremity pain from CIPS, could no longer stand for more than 10 min without the assistance of a walker [56]. Despite being administered potent opioid analgesics like oxycodone, her pain persisted at a level of 6 out of 10.

The physical limitations imposed by CIPS likely extend far beyond just mobility constraints. Unrelenting severe pain can deplete emotional reserves, strain personal relationships, disrupt sleep, and even trigger psychological conditions like depression or anxiety. The unremitting nature of the pain and symptoms may preclude patients from working or force them onto disability.

When CIPS is properly diagnosed and managed, such as by discontinuing the offending calcineurin inhibitor, the potential for regaining quality of life is immense. The case reports describe patients experiencing complete resolution of their previously devastating abdominal pain, diarrhea, and associated symptoms after tacrolimus was stopped [51]. However, effective prevention and management of CIPS remains an unmet need. The experiences documented in these case studies underscore the urgency of developing better strategies to swiftly identify and treat this rare but profoundly life-altering complication of calcineurin inhibitor therapy.

Long-term complications and sequelae of CIPS

Significant disability and reduced quality of life: several articles imply that if CIPS is not recognized and treated promptly, it can lead to significant disability and

reduced quality of life for the patient. Early recognition and appropriate management of CIPS are emphasized to prevent such long-term complications [47]. Progression to osteonecrosis (avascular necrosis): one article suggests that CIPS and transient bone marrow edema may represent earlier manifestations on a spectrum of bone disease caused by calcineurin inhibitors, with osteonecrosis being a potential long-term sequelae if the initial symptoms are not adequately treated. Prompt management of CIPS is important to prevent progression to the more severe complication of osteonecrosis, which often requires surgical intervention like core decompression or joint replacement [8].

Persistent and disabling joint pain: in one cohort study, a small percentage (2.3%) of liver transplant recipients developed CIPS, characterized by severe, long-standing joint pain that was refractory to conventional analgesics and may necessitate discontinuation of calcineurin inhibitor therapy. This highlights the potential for CIPS to cause persistent and disabling pain if not properly managed [44]. Avascular necrosis (AVN) of joints: one article reported a case where the patient developed avascular necrosis of the bilateral hip joints as a long-term complication, potentially attributed to both CIPS and prolonged corticosteroid therapy. This suggests that CIPS if left untreated, could potentially lead to the development of AVN, a severe and debilitating condition [48].

Bone density issues: one article mentioned that the patient developed borderline osteoporosis, which required calcium and vitamin D supplementation. While not directly attributed to CIPS, it suggests that bone density issues may arise in these patients, potentially contributing to long-term complications if not properly managed [57].

Reversibility of CIPS: CIPS is generally considered a reversible condition, with symptoms resolving after reducing or discontinuing the calcineurin inhibitor medication, suggesting long-term permanent complications may be unlikely if managed appropriately [1, 58].

Importance of early recognition and management: several articles emphasize the importance of early recognition and appropriate management of CIPS to prevent long-term complications and significant morbidity [8, 47, 48]. Longer follow-up needed: while CIPS is characterized as reversible, larger studies with longer follow-up periods would be needed to thoroughly evaluate the potential for any lasting effects after the resolution of acute CIPS episodes [1, 58].

Study limitations

It is imperative to acknowledge certain limitations that could impact the generalizability and depth of the findings despite our effort to provide a comprehensive review of the topic. First, there is the possibility of overlooking relevant studies not indexed in the selected databases. Furthermore, language bias may exist due to restricting the inclusion criteria to articles published in English, potentially excluding pertinent studies published in other languages and leading to an incomplete representation of the literature. Last, the potential for publication bias should also be considered, as studies reporting positive or statistically significant results are more likely to be published, potentially skewing the overall findings.

Conclusion

CIPS is a rare but disabling complication of CNI therapy, that while often self-limited, poses a considerable burden to quality of life and daily functioning. As such, there is growing interest in understanding the underlying pathophysiology, establishing robust diagnostic criteria, and exploring pharmacological and non-pharmacological treatment efficacy. Ultimately, continued investigation is warranted to assess individual variability, emphasizing early recognition and management strategies to mitigate and reduce long-term complications.

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Conceptualization of Ideas, data curation, visualization, and supervision was done by T.A.; Writing of the initial draft was done by R.E.H, J.L. M, M.W, M.L, T.M., M.H.S., A.P.M., M.K., M.Z., O.E.F., A.L.E., I.I.O.; Writing—review & editing was done by T.A., A.A. W., A.A.

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No datasets were generated or analysed during the current study.

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