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Chronic pain and infection: mechanisms, causes, conditions, treatments, and controversies

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Cite this as: *BMJMED* 2022;1:e000108. doi:10.1136/bmjmed-2021-000108

Received: 28 December 2021
Accepted: 10 March 2022

ABSTRACT

Throughout human history, infection has been the leading cause of morbidity and mortality, with pain being one of the cardinal warning signs. However, in a substantial percentage of cases, pain can persist after resolution of acute illness, manifesting as neuropathic, nociplastic (eg, fibromyalgia, irritable bowel syndrome), or nociceptive pain. Mechanisms by which acute infectious pain becomes chronic are variable and can include immunological phenomena (eg, bystander activation, molecular mimicry), direct microbe invasion, central sensitization from physical or psychological triggers, and complications from treatment. Microbes resulting in a high incidence of chronic pain include bacteria such as the *Borrelia* species and *Mycobacterium leprae*, as well as viruses such as HIV, SARS-CoV-2 and herpeses. Emerging evidence also supports an infectious cause in a subset of patients with discogenic low back pain and inflammatory bowel disease. Although antimicrobial treatment might have a role in treating chronic pain states that involve active infectious inflammatory processes, their use in chronic pain conditions resulting from autoimmune mechanisms, central sensitization and irrevocable tissue (eg, arthropathy, vasculitis) or nerve injury, are likely to cause more harm than benefit. This review focuses on the relation between infection and chronic pain, with an emphasis on common viral and bacterial causes.

Introduction

Pain is the leading cause of years lost to disability worldwide, and the most common reason for seeking healthcare.[1 2] Teleologically, pain serves as an existential protective mechanism against internal and external stimuli that threaten an organism, with evidence that even the most primitive organisms experience nociception, including fish and invertebrates.[3]

Throughout history, infectious diseases have exacted the greatest toll on humankind in terms of morbidity and mortality, and dolor (pain) is a cardinal sign of infection.[4] Although our bodies eradicate most infections, a substantial percentage will persist in a sublethal or lethal form because of failure in detection or treatment (table 1). In other individuals, an infection could resolve but trigger an enduring immune response that results in chronic pain, which can occur in 10-33% of cases of nociplastic and post-infectious pain syndromes, or serve as a psychological stressor that initiates or exacerbates chronic pain.[5–8] The inextricable link between chronic pain and infection is illustrated in a recent study evaluating nearly 2 million patients with covid-19, which found chronic pain to be the most common lingering complaint at least 30 days after diagnosis, affecting 5.1% of the 23% of patients with so-called long haul symptoms.[9] To date, a comprehensive analysis on chronic pain syndromes after infection has yet to be undertaken.

Sources and selection criteria

Between September 2021 and January 2022, we searched the following databases for articles pertaining to chronic pain and infection: PubMed, Embase, OVID, and Google Scholar, without language or date restrictions. We cross referenced the major search terms "chronic pain," "pain," "vaccine," "antibiotic," "antiviral," "mechanism," "infection," and "complication" with various iterations and subcategories of these keywords to correspond with various pathogens, drug treatments, mechanisms (eg, "bystander activation"), and chronic pain conditions. We prioritized peer reviewed systematic reviews and large clinical trials, but included narrative reviews, case series, and retrospective studies as indicated. In addition to primary sources, we searched reference lists of retrieved articles.

Mechanisms

Acute pain

Infection can cause pain via numerous mechanisms. Acutely, pain is a core symptom of infection, and could result directly from somatic (eg, septic arthritis) or visceral (eg, appendicitis) tissue invasion, or nerve injury (eg, acute herpes zoster neuritis) and the accompanying inflammatory process.

Chronic pain

Molecular mimicry and other immune mechanisms

Figure 1 shows the various mechanisms by which chronic pain can occur after infection. Inflammation after infection might cause an abnormal immune response that triggers acute and chronic neuropathic, nociceptive, or nociplastic pain. In Guillain-Barré syndrome, immunoglobulin G induced, painful peripheral neuropathy affects between 55% and 89% of individuals, with two thirds of patients experiencing a viral (eg, Epstein-Barr virus, Zika virus) or bacterial (eg, *Campylobacter jejuni*) infection within

Table 1 | Pain syndromes commonly associated with infectious causes[115 189–191]

	Pain classification					
		Nociceptive pain				
			Somatic pain		Nociplastic pain	
Variable	Neuropathic pain	Visceral pain	Myositis and myopathy	Arthritis, arthropathy, and others	Fibromyalgia	Others
Common infectious agents	Viruses: varicella zoster virus, flaviviruses (eg, West Nile virus, dengue virus, hepatitis C), herpesviruses (eg, herpes simplex virus, Epstein-Barr virus, cytomegalovirus), HIV, human T lymphotropic virus 1 Bacteria: *Borrelia burgdorferi* (Lyme disease), *Brucella* species, *Corynebacterium diphtheriae*, *Mycobacterium* species (leprosy, tuberculosis)	Hepatitis: hepatitis viruses A-E Myocarditis: coxsackieviruses, parvovirus, SARS-CoV-2, adenovirus, HIV, herpes simplex virus, Epstein-Barr virus, cytomegalovirus, *Trypanosoma cruzi* (Chagas disease) Gastritis, peptic ulcers: *Helicobacter pylori* Cholecystitis: *Enterobacteriaceae*, cytomegalovirus, *Clonorchis sinensis*, *Ascaris lumbricoides* Pelvic: *Chlamydia trachomatis*, *Neisseria gonorrhoeae*	Viruses: coxsackie B virus, Epstein-Barr virus, hepatitis B and C, HIV, human T lymphotropic virus 1, influenza A and B Bacteria: Gram positive (eg, *Staphylococcus aureus*, group A *Streptococcus*), Gram negative (eg, *Escherichia coli*, *Proteus* species, *Pseudomonas* species, *Salmonella* species), anaerobes (*Bacteroides* species, *Clostridium* species), *Mycobacterium* species, *Brucella* species, *Mycoplasma pneumoniae* Fungi: *Candida* species Parasites: *Plasmodium* species, *Trichinella* species	Arthropathy: parvovirus B19, hepatitis viruses, chikungunya virus, rubella, alphaviruses, flaviviruses, and retroviruses Low back pain: *Cutibacterium acnes*, coagulase negative *Staphylococcus*	Viruses: HIV, Epstein-Barr virus, hepatitis viruses, influenza, SARS-CoV-2 Bacteria: *Borrelia burgdorferi*	Irritable bowel syndrome: *Salmonella*, *Shigella*, *Escherichia coli*, *Campylobacter jejuni* Interstitial cystitis or bladder pain syndrome: controversial, but *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Corynebacterium* infection could be more common in certain phenotypes. Myalgic encephalitis or chronic fatigue syndrome: Epstein-Barr virus, cytomegalovirus, human herpes viruses 6 or 8, parvovirus B19, enteroviruses, lentivirus, SARS-CoV-2, *Mycoplasma*, *Borrelia* species, *Coxiella burnetii* Chronic pelvic pain: *Chlamydia trachomatis*, *Neisseria gonorrhoeae*
	Encephalitis: herpes simplex viruses and other herpesviruses, enteroviruses (eg, coxsackievirus, poliovirus), mosquito borne viruses (eg, West Nile, western equine, and eastern equine encephalitis), rabies virus, measles, mumps, rubella					
Presentation	Often described as lancinating or shooting. Numbness and dysesthesias present in stocking-glove or nerve distribution (eg, mononeuropathies). Weakness can be neurological or pain induced.	Dull, aching, often poorly localized. Gastrointestinal visceral pain is often associated with a strong affective component including emotional triggers. Neurological symptoms are uncommon except with encephalitis.	Myositis often occurs with skin manifestations (eg, dermatomyositis). Most commonly affects the shoulders, hips, and thighs. Presents with diffuse, aching pain and weakness, often associated with activities and exertion.	Arthropathy: most commonly affects the shoulders, hips, and knees. Aching pain, often worse with activity and accompanied by tenderness, stiffness, oedema, and effusion. Radiographs typically reveal degenerative changes. Focal neurological symptoms are uncommon. Back pain: diffuse aching pain that might radiate in a non-dermatomal distribution into the proximal lower extremities, worse with activity and sitting. No focal neurological findings, although radiculopathy is more common in patients with disc degeneration.	Widespread pain, often concomitant with other nociplastic conditions including non-specific spinal pain. Somatic symptoms and hypersensitivities are frequently present (eg, bowel and urinary symptoms, dyspareunia, photosensitivity, phonosensitivity). Sensory deficits might be present but in a non-anatomical distribution. Paroxysms of pain are often related to psychological stressors.	Often described as cramping (irritable bowel syndrome), aching, sharp, and diffusely localized. High co-prevalence with other nociplastic conditions. Somatic symptoms and hypersensitivities are frequently present.

Continued

Table 1 Continued

Variable	Pain classification					
	Nociceptive pain				Nociplastic pain	
			Somatic pain			
	Neuropathic pain	Visceral pain	Myositis and myopathy	Arthritis, arthropathy, and others	Fibromyalgia	Others
Treatments	Antimicrobial treatment and nutrient supplementation are not proven to reverse longlasting neuropathology, but might be effective in preventing or even reversing neuropathies in some cases with high microbial loads. Although weak evidence supports some individual treatments (eg, high concentration capsaicin and acetyl-L-carnitine for HIV neuropathy), treatments should generally be based on established neuropathic pain treatment algorithms.	Typically supportive care and appropriate treatment of underlying infection will alleviate pain symptoms. Antimicrobial agents are highly effective for *H pylori*, acute bacterial cholecystitis, and early in Chagas disease.	Antimicrobial treatment could be effective for acute pain, but not for chronic pain secondary to immunological mechanisms. Antidepressants and non-steroidal anti-inflammatory drugs might provide some relief. Immunosuppressant treatment can be considered on a case-to-case basis (eg, immunoglobulins).	Arthropathy: long term antimicrobial treatment might be effective for acute pain, but not chronic pain secondary to immunological mechanisms. Steroid injections are contraindicated in acute infection but might provide benefit in immune mediated arthropathy with active inflammation. Joint replacement could be indicated in immune mediated arthropathy without concomitant infection. Antidepressants and non-steroidal anti-inflammatory drugs might provide some relief; immunosuppressant treatment can be considered on a case-to-case basis. Back pain: antibiotics might be effective if characteristic, vertebral endplate signal changes are present, but must be given for a prolonged duration due to poor intradiscal penetration. Antidepressants and non-steroidal anti-inflammatory drugs can be considered if appropriate. Most interventional treatments for discogenic low back pain are characterized by high failure rates.	Mechanisms for infection-induced fibromyalgia do not support antimicrobial treatment. Reducing risk factors for widespread pain (eg, poor sleep, low activity levels, and psychological distress) could reduce incidence. Drug treatments similar to those for neuropathic pain, with supportive measures (eg, improved sleep hygiene, low impact aerobic exercise, psychotherapy) provided as needed.	Antibiotics such as rifaximin and neomycin might be effective for irritable bowel syndrome from small intestine bacterial overgrowth. Some evidence for probiotics, but sparse evidence for prebiotics. Scant evidence for antibiotics in longstanding bladder pain syndrome. Intravesical treatment might be indicated in some patients. Other treatments for nociplastic pain syndromes include supportive treatments and pharmacotherapy (eg, antidepressants).

the preceding six weeks.[10–12] The precise mechanisms for axonopathy are unclear, but evidence points to mimicry of axolemmal surface molecules (gangliosides) by microbial antigens (lipopolysaccharides), leading to an antibody mediated attack on the nerve axolemma. Other immune related painful conditions in which molecular mimicry is postulated to have a role include multiple sclerosis, reactive arthritis, inflammatory bowel disease, and Lyme disease. Similarly, infection could trigger autoimmune related pain via epitope spreading and bystander activation. In epitope spreading (also known as antigen spreading), endogenous epitopes develop secondary to the release of self-antigens during inflammation.[13] Bystander activation is characterized by autoreactive B and T cells that are activated in an antigen independent manner.[14]

Viral gene products or remnants

Preclinical studies have shown that products produced by viral infections could enhance pain

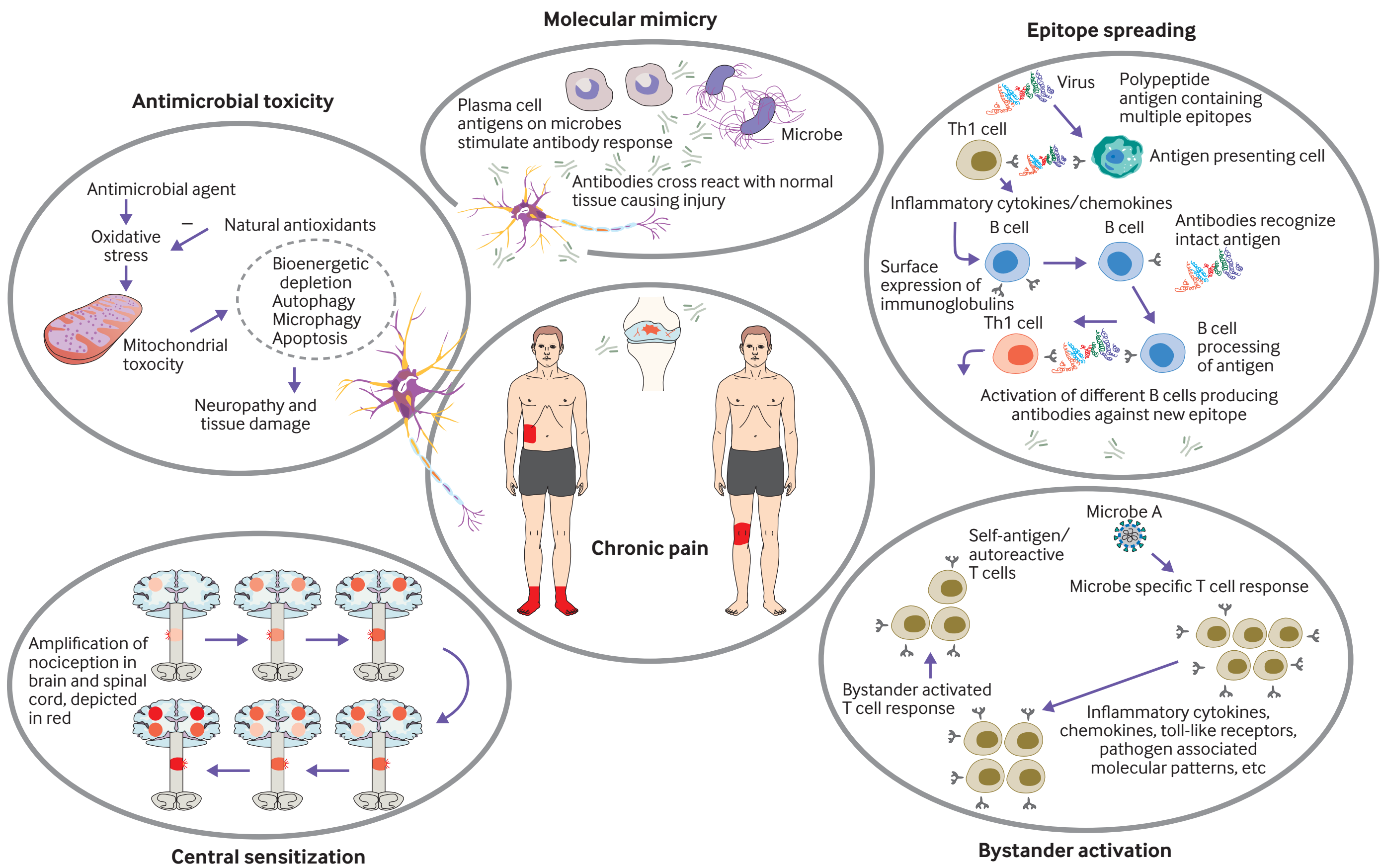

Figure 1 | Mechanisms of chronic pain after infection

sensitivity. In rodents, elevated levels of the inflammatory enzyme indoleamine-2,3-dioxygenase heighten pain sensitivity, which returns to normal as the infection clears, or remains elevated with persistent infection (eg, murine leukemia retrovirus, an analogue of human immunodeficiency virus (HIV)-1).[15] These findings are consistent with studies demonstrating increased pain sensitivity in people living with HIV with detectable viral loads compared with controls without HIV or with HIV without detectable virus loads.[16] Persistent infection and resultant peripheral and central sensitization might be particularly common with herpes viruses (eg, Epstein-Barr virus, cytomegalovirus, human herpes viruses 6 and 7), which can remain dormant for years and are a common antecedent for myalgic encephalitis or chronic fatigue syndrome, which is frequently characterized by diffuse chronic pain. Retroviruses such as HIV and human T cell lymphotropic virus type 1, which integrate into the genome, might also contribute to persistent symptoms and sensitization.[17–19] Diffuse, chronic pain is a hallmark of most diagnostic criteria for myalgic encephalitis or chronic fatigue syndrome, and active HIV infection is associated with myriad neuropathic, nociceptive, and nociplastic pain symptoms, suggesting viral induced central sensitization.[20 21] Similarly, viral remnants such as mRNA or proteins, or even subdetectable levels of virus, could promote a persistent immune response which results in pain and other symptoms typically associated with acute infections.[22]

Treatment associated chronic pain

Vaccine reactions—Vaccines are designed to induce an immune response. After entering the body, antigen derived (pathogen associated) and host derived (damage associated) molecular patterns bind to pattern recognition receptors such as toll-like receptors found on circulating immune and stromal cells. This event results in transcription of target genes leading to the synthesis and release of inflammatory cytokines (eg, interleukin 1, interleukin 6, tumor necrosis factor alpha). An immunologic cascade is initiated, mimicking an attenuated response to infection, leading to phagocytosis, release of acute phase reactants, and further release of inflammatory mediators including chemokines and cytokines, complements, and leukocytes.[23] The local production of inflammatory mediators can lead to site specific pain, while systemic circulation can result in diffuse symptoms that include headache, myalgias, arthralgias, and rarely neurological symptoms.[23 24] Although very rare, long term sequelae of certain vaccinations have been reported including persistent localized pain at the inoculation site and Guillain-Barré syndrome.[25 26]

Table 2 | Antimicrobial drug treatments associated with neuropathy and other pain conditions[192–194]

Drug treatment	Common indications	Associated pain conditions	Comments
Antibiotics			
Chloramphenicol	Superficial eye and ear infections, typhoid, cholera, meningitis	Peripheral neuropathy, bowel inflammation	Broad spectrum antibiotics are rarely used in Europe and North America owing to the potential for aplastic anemia, and designation by the World Health Organization as a probable human carcinogen.
Chloroquine and hydroxychloroquine	Malaria, amoebiasis, rheumatic diseases	Peripheral neuropathy, myopathy	Chronic pain conditions are associated with long term use for rheumatic conditions.
Clioquinol	Fungus and protozoan infections; sometimes mixed with other agents for inflammatory skin conditions	Peripheral neuropathy and spinal cord demyelination	Development of subacute myelo-optic neuropathy led to ban in many countries. Resurgence in study for cancer and neurodegenerative disorders.
Dapsone	Leprosy, *Pneumocystis* prophylaxis, dermatitis herpetiformis	Peripheral neuropathy, internal organ inflammation (nephritis, interstitial pneumonitis, hepatitis)	Common alternative to trimethoprim-sulfamethoxazole for *Pneumocystis* prophylaxis in immunocompromised patients.
Ethambutol	Tuberculosis and non-tuberculous mycobacterial infections	Peripheral and optic neuropathy, worsening gout or joint pain, hepatitis	Used in combination with other drugs to treat tuberculosis and non-tuberculous mycobacterial infections, often for many months.
Fluoroquinolones	Broad spectrum, effective against many bacteria, including tuberculosis and non-tuberculous mycobacterial infections	Peripheral neuropathy, tendinopathy, myopathy and arthropathy, hepatitis	Associated with four black box warnings (tendon rupture or tendonitis, peripheral neuropathy, effects in the central nervous system, exacerbation of myasthenia gravis).
Griseofulvin	Ringworm (tinea) infections including athlete's foot (tinea pedis)	Peripheral neuropathy, myopathy and arthropathy, hepatitis	Treatment duration could last from weeks to months, usually after topical treatments have failed.
Isoniazid	Tuberculosis (active and latent) and non-tuberculous mycobacterial infections	Peripheral neuropathy, myopathy, hepatitis, lupus-like syndrome with polyarthralgia and erythematosus	Used in tandem with other anti-tuberculosis drugs, often for many months. Neuropathy could be prevented by co-treatment with pyridoxine.
Linezolid	Gram positive bacteria, multidrug-resistant tuberculosis and non-tuberculous mycobacterial infections	Peripheral and optic neuropathy, diffuse body aches, hepatitis, and abdominal pain	Prolonged courses generally needed for tuberculosis and non-tuberculous mycobacterial infections. Incidence of neuropathy might be reduced by once daily dosing.
Metronidazole	Anaerobic bacteria, parasitic infections such as amoebiasis and trichomonas	Peripheral neuropathy, oral ulcers or stomatitis, cystitis, dysuria and pelvic pain, proctitis	Often used for sexually transmitted diseases and after colorectal surgery.
Nitrofurantoin	Broad spectrum, commonly used in urinary tract infections	Peripheral and optic neuropathy, interstitial pneumonitis, hepatitis	Side effects are less common because the drug concentrates in urine; drug resistance is uncommon.
Suramin	Antiparasitic used to treat trypanosomiasis (African sleeping sickness) and onchocerciasis (river blindness)	Peripheral neuropathy, arthralgia (suramin also inhibits osteoarthritic cartilage degradation)	Has demonstrated efficacy for hormone refractory prostate cancer and autism; introduced 100 years ago in 1922.
Antiviral drug treatments			
Zalcitabine	HIV	Peripheral neuropathy, hepatitis, pancreatitis, stomatitis, myopathy	Neuropathy from nucleoside reverse transcriptase inhibitors might be exacerbated by alcohol use, metabolic impairments, co-treatment with other nucleoside reverse transcriptase inhibitors, and low CD4 counts. Incidence ranges from 30% to >75%. Rarely used in developed countries.
Didanosine	HIV	Peripheral neuropathy including optic neuritis, myopathy, pancreatitis and other gastrointestinal symptoms (eg, hepatitis)	Co-treatment with stavudine should be done with caution owing to high risk of side effects. Side effects are dose related and usually reversible. Treatment course could last for years. Rarely used in developed countries
Stavudine	HIV	Peripheral neuropathy, pancreatitis, lactic acidosis	Treatment course could last for years. Side effects are dose related and usually reversible. Rarely used in developed countries
Zidovudine	HIV and prevention of perinatal HIV transmission	Myopathy, headache, hepatitis	Treatment course could last for years. Side effects are dose related and usually reversible. Rarely used in developed countries
Nevirapine	HIV	Hepatitis, peripheral neuropathy, gastrointestinal symptoms	Non-nucleoside reverse transcriptase inhibitor. Elevated liver enzymes much more common than hepatitis. Increased risk of hepatitis in individuals with infectious hepatitis.
Etravirine	HIV	Hepatitis, peripheral neuropathy, gastrointestinal symptoms including pancreatitis, toxic epidermal necrolysis	Non-nucleoside reverse transcriptase inhibitor. Treatment course could last for years. Incidence difficult to pinpoint in clinical trials evaluating multiple concurrent drug treatments.
Lamivudine	HIV and hepatitis B	Peripheral neuropathy, pancreatitis, myopathy	Peripheral neuropathy is generally mild, usually with other nucleoside reverse transcriptase inhibitors during long term treatment.
Fialuridine	Hepatitis B (not currently in use)	Peripheral neuropathy, myopathy	1993 clinical trial at the US National Institutes of Health halted because over one-third of patients developed liver failure.

Antimicrobial and surgical treatment—antibiotics and antiviral treatments could be associated with chronic pain conditions such as peripheral neuropathy, usually in dose dependent or time dependent fashions. An association between antibiotic use and peripheral neuropathy has also been found for other drugs (table 2). Mechanisms of antibiotic induced neuropathy might include axonal toxicity, demyelination, and conduction blockage.[27]

Antiviral drug treatments such as nucleoside analogue reverse transcriptase inhibitors and interferon α might be prescribed for a prolonged time for infections with HIV and hepatitis, increasing the likelihood of toxicity. Nucleoside reverse transcriptase inhibitors such as didanosine and stavudine could cause myopathy characterized by muscle wasting, myalgia, weakness, and elevation of creatine kinase, as well as a dose dependent neuropathy that is painful and axonal in nature.[28] Other pain conditions associated with antimicrobial drug treatments include vasculitis, encephalitis, arthralgia, and headache.

Surgical tissue removal and other procedures might be used to treat infection, including appendicitis, cholecystitis (>50% are secondary to infection), and necrotizing fasciitis. The prevalence of chronic pain after surgery has been cited at around 18% in children after appendectomy[29] and 14% after cholecystectomy, although about 33% of patients will continue to report persistent painful symptoms after gallbladder resection.[30]

Common viral related neuropathic pain conditions

Neuropathic pain is defined by the International Association for the Study of Pain as "pain caused by a lesion or disease of the somatosensory nervous system,"[31] and is recognized as being mechanistically distinct from nociceptive pain and nociplastic pain.[32 33] Viral infections can lead to neuropathic pain by creating lesions in the peripheral or central nervous system,[32 34] producing cytokines that sensitize nociceptors,[35] or eliciting an immune response that attacks organ systems.[12–14] Although viruses can also cause nociceptive pain (eg, arthritis), pathogenesis is varied and pathogen specific.[36]

Varicella zoster virus

Varicella zoster virus is responsible for chickenpox and shingles. After a primary infection, it lies dormant in a dorsal root or cranial ganglion and reactivates upon a decline in immunity. Pain can be spontaneous, paroxysmal, or evoked (eg, allodynia), and acute reactivation typically causes nociceptive (vesicular rash) and neuropathic (acute radiculitis) pain.

Postherpetic neuralgia is the most common and one of the most serious complications of acute infection with varicella zoster virus, and is defined as pain persisting more than 90 days after the onset or healing of the vesicular rash.[37] Mechanisms include nerve root inflammation and ectopic discharges, peripheral sensitization, and central sensitization (eg, loss of inhibitory neurons, glial cell activation), deafferentation in the affected dermatome, and central nervous system reorganization (eg, alterations in brain metabolism, decreased grey matter, and sympatho-afferent coupling).[38]

Postherpetic neuralgia can eventually develop in approximately half of the individuals infected with varicella zoster virus.[37] Risk factors include older age, prodromal pain, severe acute pain or rash, marked immunosuppression, and diabetes.[37 39 40] Because greater acute pain and rash severity might indicate increased neural damage,[40 41] treatment of varicella zoster virus and resultant acute pain could reduce the incidence of postherpetic neuralgia. Strategies have included antiviral treatment, steroids, non-steroidal anti-inflammatory drugs, neuropathic analgesics, local anesthetics, epidural steroids, and neuromodulation.[42–46] However, these treatments have yielded mixed results for the prevention and treatment of postherpetic neuralgia. Vaccination is the most effective means of preventing postherpetic neuralgia, reducing risk by up to 67%, and vaccinated patients who do develop the disorder have less severe symptoms.[47]

Human immunodeficiency virus (HIV)

More than 30 million individuals worldwide are infected with HIV type 1 (HIV-1) or 2 (HIV-2),[48] although this number is likely an underestimate because of poor access to healthcare among populations at risk.[49 50] Six strains of HIV-1 account for the vast majority of infections globally.[51] HIV-2 is characterized by lower transmissibility and is uncommon outside West Africa.[51 52]

With the development of antiretroviral treatments, the prognosis of HIV infection has markedly improved and many patients have a near-normal lifespan. However, antiretroviral drugs rarely eliminate the virus entirely. As a consequence of chronic infection, more than 50% of individuals with HIV develop chronic non-cancer associated pain.[53 54] Painful peripheral neuropathy is one of the most common symptoms, with the most form having a characteristic stocking-and-glove distribution.[53 55] HIV can directly cause neural damage via certain components of its viral envelope, such as glycoprotein 120, that induce axonal degeneration, inflammatory cytokine release, and increased oxidative stress.[56 57] Earlier generations of antiretroviral drug treatments were associated with distal polyneuropathies,[53] possibly through the upregulation of inflammatory cytokines, microglial activation, and direct neuroinflammation.[58 59] Cohort studies performed before the advent of highly active antiretroviral treatments found an increased incidence and severity of polyneuropathy in individuals who are immunosuppressed and with higher viral loads, with some evidence that effective treatment might be associated with improvement in pain and other neurological symptoms.[60 61]

HIV infection is also associated with a greater risk of concomitant nociceptive or nociplastic pain. Patients with HIV commonly report abdominal pain, chest pain, musculoskeletal pain, and headaches,[53 55] and are at higher risk of developing fibromyalgia.[55] How HIV directly leads to these symptoms is unclear, but mechanisms similar to the development of neuropathic pain, including central and peripheral sensitization and psychosocial factors (eg, social isolation or stigma), are likely to be involved.[55]

Herpes simplex virus

The vast majority of people worldwide are infected with either herpes simplex virus type 1 (HSV-1) or 2 (HSV-2).[62] Infection occurs through contact with mucosal surfaces or abraded skin. Although acute symptoms might occur,[63] most individuals are asymptomatic.[62] HSV-1 and HSV-2 enter sensory ganglia and establish lifelong latency.[62 64] Cycles of dormancy and reactivation can occur, most commonly at mucocutaneous sites[63 64] (eg, vesicular lesions at the vermilion border of the mouth, herpetic whitlow in medical and dental professionals' fingers), often with prodromal burning, itching, or pain.[63]

Highly morbid painful neurological manifestations can occur. HSV-1 is associated with encephalitis[63 65] and herpes keratitis, which presents with ocular pain and is one of the leading causes of infectious blindness in the world.[66] Owing to its ability to establish latency in the cranial ganglia, HSV-1 might also lead to Bell's palsy, which is sometimes characterized by pain.[65] HSV-2 is associated with meningitis, ascending thoracic or lumbosacral myelitis, and lumbosacral radiculitis, and might have a synergistic relation in causing these symptoms in patients with HIV.[65] HSV-1 and HSV-2 might also cause central spontaneous pain via glial activation, although the incidence and mechanism(s) are unclear.[64] Antiviral drug treatments could reduce the severity and duration of symptoms, but do not eradicate the virus.

Hepatitis C virus

Hepatitis C virus is a member of the *Flaviviridae* family with up to 190 million individuals worldwide infected.[67 68] The virus replicates up to 10 trillion copies per day without a proofreading mechanism, leading to numerous genetic variants that prevent the host's immune system from eradicating it.[67] Hepatitis C virus has the distinction of being the hepatitis virus with the most known extrahepatic manifestations,[69] including arthralgia, lymphoma, type diabetes, and chronic kidney disease. Most of these conditions are independently associated with chronic pain.

The virus is also the leading cause of mixed cryoglobulinemic vasculitis, which can lead to a distal sensory or sensorimotor peripheral neuropathy that presents with painful paresthesias.[69 70] Peripheral neuropathy can occur independently of cryoglobulinemia and might be more strongly associated with older age and the duration of infection with hepatitis C virus.[68 71] Evidence also suggests that the virus can elevate levels of inflammatory cytokines such as interleukin 6, contributing to hyperesthesia and possibly centrally mediated pain.[72]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Covid-19 is associated with acute pain in 20% to >60% of patients admitted to hospital, with the most common complaints being myalgia or arthralgia, headache, and sore throat (≥25%); followed by chest pain, spinal pain, abdominal pain, and non-headache neurological symptoms.[73–75] These symptoms can result from a combination of factors, including a hypervigilant immune response, fever, deconditioning, and direct viral invasion (arthralgia, myositis, myocarditis or chest pain).[75 76] Although SARS-CoV-2 is not primarily neurotropic, the virus binds to angiotensin converting enzyme 2 receptors in the central and peripheral nervous system, and has been linked to myelitis, Guillain-Barré syndrome, and peripheral neuropathy.[75 77] As with other viral mediated illness, neuropathic pain can be triggered by immune mechanisms, antiviral treatment, or direct viral invasion, and carries a higher incidence in those individuals with pre-existing risk factors (eg, diabetes).[78] About 5-15% of patients admitted to hospital with covid-19 will present with abdominal pain, which might be secondary to viral binding to angiotensin converting enzyme 2 receptors in the gastrointestinal tract, lymphadenopathy, referred pain from the lungs, or visceral distension.[75]

In one observational study, the presence of acute pain was paradoxically found to mitigate against death and intensive care, which was attributed to the activation of neurotransmitters involved in pain modulation and distraction.[74] In another case-control study, patients who experienced myalgia during acute covid-19 had a greater likelihood of having musculoskeletal pain seven months after covid-19 infection that those who did not have myalgia (odds ratio 1.41, 95% confidence interval 1.04 to 1.90).[79] Several studies have found chest pain, headache, myalgias, and arthralgias to be present in over 20% of surviving patients with covid-19, 60 days after infection, with neuropathy, spinal pain, and abdominal pain reported less frequently.[80] Since patients in these studies did not have measurable viral loads, the cause of these symptoms is likely immunological or a psychological triggering event.[5]

Common bacterial related pain conditions

Borrelia burgdorferi (Lyme disease)

Lyme disease results from infection with several *Borrelia* species including *burgdorferi*, *afzelii*, and *garinii*. Pain can appear immediately after infection (stage 1 includes, for example, localized pain and constitutional symptoms), days to weeks after infection (stage 2 includes, for example, severe headache, myalgias and arthralgias), and during a controversial stage 3, which can range from months to years after infection and has been postulated to be secondary to central sensitization.[81 82]

About 10-20% of patients with infection develop post-treatment Lyme disease syndrome, which entails unequivocal evidence of infection and appropriate treatment. However, in one analysis of seven observational and retrospective studies including 1902 patients in endemic areas, 50-88% of enrolled patients had no evidence of *Borrelia* infection.[83] The cause is most likely autoimmune, with high antibodies to *Borrelia burgdorferi* found in some patients with reactive arthritis.[83 84] Diffuse pain is a hallmark, with over 75% of individuals reporting headache, arthralgias, myalgias, neuropathic pain, and widespread pain most consistent with nociplastic pain. Similar to other nociplastic conditions, sensory hyperarousal, cognitive deficits, fatigue, and sleep dysfunction also affect most individuals with post-treatment Lyme disease syndrome.[85] Although antibiotics are frequently prescribed and have been found in some studies to provide subjective benefit,[85 86] the Centres for Disease Control and Prevention recommends against their routine use based on high quality trials.[87]

Mycobacterium leprae (leprosy)

Leprosy, also known as Hansen's disease, causes 250 000 infections worldwide annually, with Brazil, India, and Indonesia accounting for 80% of cases.[88] The bacterium responsible for leprosy, *Mycobacterium leprae*, is morphologically indistinguishable from *Mycobacterium tuberculosis*. In 1982, the World Health Organization developed a simple classification system, which categorizes patients as having paucibacillary (≤5 lesions) or multibacillary (≥6) leprosy, reflecting the tissue burden of the infection.[89]

Although sensory loss, visual impairment and disfigurement are more notorious, neuropathic pain is present in about 35% (range 11-66%) of patients. with leprosy[90–92] The bacterium can enter the nervous system via endothelial cells or transmigration of infected monocytes, showing an affinity for Schwann cells. The type of neuropathic pain varies based on disease burden, with the ulnar and peroneal nerves commonly affected in paucibacillary leprosy, while advanced stages frequently result in a diffuse symmetrical polyneuropathy that often includes the facial and trigeminal nerves.[92] In addition to neuropathic pain, patients with leprosy also experience nociceptive pain from tissue invasion (eg, skin, nose, testicles) and disfigurement, with lifetime prevalence rates ranging from 15 to >40%.[93–95] Patients with leprosy also have disproportionate psychological distress including ostracization and stigmatization, which can exacerbate pain. Although corticosteroids are often used to treat acute neuritis from leprosy, a systematic review found no evidence for long term superiority over placebo for nerve function.[93 96] Because most neuropathology in leprosy is immunological, nerve injury and neuropathic pain can occur before, during, or after antibiotic treatment.[97]

Group A streptococcus

In acute rheumatic fever, oropharyngeal group A streptococcus infection triggers an autoimmune response resulting in inflammation and organ damage.[98] Most patients who develop rheumatic fever are aged between 5 and 15 years, with *Streptococcus pyogenes* being the most implicated bacterial strain. In one large database study of 1470 children, 50% of rheumatic fever hospital admissions presented with primary arthritis without carditis, 26% presented with arthritis and carditis, 24% presented with chorea, and 6.5% showed both chorea and carditis.[99] Recurrences are common in rheumatic fever, especially in younger individuals. Considered by many to be a prototypical autoimmune condition, rheumatic fever can manifest as a prolonged pain syndrome that includes reactive polyarthritis, skin involvement, carditis, vasculitis, and chorea, which might result in associated neurologic symptoms including pain.[98 100] About 5% of patients with untreated, group A streptococcus pharyngitis develop rheumatic fever, with early antibiotic treatment reducing the risk substantially. Prophylactic antibiotics are recommended to prevent recurrences.[101]

Treponema pallidum

Treponema pallidum is a spiral-shaped bacterium belonging to the phylum Spirochaetes, with subspecies that each cause a distinct disease (*T pallidum* subspecies *endemicum*, *T carateum*, and *T pallidum* subspecies *pertenue* cause bejel, pinta, and yaws, respectively).[102 103] These subspecies are serologically and morphologically indistinguishable,[103 104] spread by direct contact through dermal microabrasions or mucosal membranes, and form painful mucocutaneous ulcers. However, *T pallidum* subspecies *pallidum*, the causative agent of syphilis, is unique in being transmissible via blood and is most commonly spread through sexual contact.

Humans are the only known natural host of *T pallidum* subspecies *pallidum*.[102] With the introduction of penicillin, the incidence of syphilis declined considerably in the mid-20th century.[105] However, cases have steadily increased over the past 20 years in association with unsafe sexual practices (eg, unprotected sexual contact, promiscuity), with WHO estimating 12 million new cases annually across the globe.[102]

On infection, systemic dissemination occurs within hours, and a painless chancre—the characteristic sign of primary syphilis—appears within three weeks.[102] Within three months, secondary syphilis occurs, which is characterized by a disseminated maculopapular rash and protean findings[105] that can be associated with pain and discomfort, including lymphadenopathy, mucosal lesions, gastritis,[106] hepatitis,[107] glomerulonephritis,[108] and pulmonary abscesses.[109] After a latent period that is usually less than a year, tertiary syphilis begins. Neurologic manifestations are most common (eg, paresthesias, paresis, and ataxia from tabes dorsalis,[102] vision loss,[110] and cognitive impairments[105]), followed by cardiovascular complications (eg, aortic aneurysm and myocarditis) and granulomatous nodules known as gummas.[102 105] Regardless of the stage of infection, penicillin is the treatment of choice,[105] although even with bacterial eradication, pain could persist when organ damage is severe.

Infection and nociplastic pain

In 2016, the term "nociplastic pain" was proposed to describe pain characterized not by nerve or tissue injury, but by alterations in pain related sensory pathways leading to peripheral and central sensitization.[33] Fibromyalgia is the prototypical nociplastic pain condition, but similar syndromes such as irritable bowel syndrome, bladder pain syndrome, and chronic daily headache are also considered nociplastic.

Cohort and cross-sectional studies have found that between 6% and 27% of patients with fibromyalgia report an infectious inciting event (eg, Epstein-Barr virus, Lyme disease), with up to 40% describing worsening symptoms after infection.[111 112 113] In small case-control study, researchers contacted 22 (of 50) patients unable to return to work after severe acute respiratory syndrome (SARS); they found striking similarities to 21 female controls with fibromyalgia, and a strong overlap with chronic fatigue syndrome (CFS).[114] For irritable bowel syndrome, one review reported an unweighted median in 10 studies of 10% (range 4-32%) for an infectious etiology, with the most common causes being gut pathogens (*Escherichia coli*, *Shigella*, *Campylobacter, Salmonella*).[115] The high incidence of recurrent urinary tract infections in women and the overlap in symptoms between urinary tract infections and bladder pain syndrome (interstitial cystitis) make conclusions difficult to draw regarding an infectious cause, with clinical studies yielding mixed results.[7 116] Currently, the absence of an ongoing infection is an exclusion criterion for bladder pain syndrome. For chronic daily headache (and to a lesser extent migraines), some studies of various designs report that over 20% began with an infection, although results are mixed.[117–119] Some interventional studies also report the alleviation of symptoms when bacterial organisms such as Helicobacter Pylorii are eradicated.[120] While rare and anecdotal, nociplastic symptoms such as diffuse body pain and persistent headaches have also been reported after vaccinations.[121 122] In addition to sensitization from post-inflammatory immune reactions, region-specific causes include changes in gut microbiota and injury to enteric nerves for irritable bowel syndrome, and low grade encephalomyelitis for headaches.

Influence of postoperative infection on persistent pain after surgery

Persistent pain after surgery occurs in 10-50% of patients experiencing acute postoperative pain, with 2-10% reporting severe chronic pain.[123 124] Chronic pain after surgery might result from peripheral and central pain sensitization due to inflammation, tissue damage, and nerve injury.[124 125] Tissue damage and nerve injury occurring as a direct result of surgery can trigger localized and systemic inflammation in a mechanism similar to, but independent from, perioperative pathogenic infection.[125 126] Patients undergoing surgery are also vulnerable to healthcare associated infections. About 7% of patients undergoing surgery have an infection during the perioperative period, resulting in substantial morbidity, mortality, and healthcare costs.[127 128] Exogenous infection can compound the mechanisms of neuroinflammation and systemic inflammation that lead to chronic pain after surgery. Risk factors for persistent pain after surgery include preoperative pain, acute postoperative pain intensity and the extent of nerve and tissue damage, all of which can be amplified by infection.[124 129] In addition, patients' specific immune function and inflammatory responses have been shown to correlate with surgical recovery, including postoperative pain and function.[130–133]

Few studies have evaluated the relation between postoperative infection and chronic pain, and few guidelines draw any explicit connection between the two. Most often, infection is considered as an alternative diagnosis for chronic pain after surgery. The International Association for the Study of Pain's classification notes that "other causes of pain such as pre-existing pain conditions or infections... have to be excluded in all cases of chronic post-traumatic and post-surgical pain."[134] However, pain is a common feature of infection after surgery,[135] and the presence of infection could provide sufficiently prolonged afferent stimulation to result in sensitization, a key mechanism underlying the transition from acute to chronic pain after surgery.[136]

A retrospective cohort analysis of nearly 12 000 adults undergoing surgery found that surgical wound infection or sepsis was the most common major postoperative complication, and was associated with a 1.53 times increased odds (95% confidence interval 1.18 to 2.05) of lingering pain after surgery, after adjusting for confounding variables.[137] These findings are consistent with observational studies reporting a higher incidence of persistent pain after surgery in patients with wound complications after sternotomy[138] and infection after hysterectomy.[139] A recent meta-analysis of 18 prospective and retrospective gynecological and urological surgery studies found that surgical wound infection was associated with a 2.71 times (1.75 to 4.18) increased risk of persistent pain after surgery.[140] Postoperative infection should therefore be considered a risk factor for persistent pain after surgery, not just an alternative diagnosis.

Risk factors for surgical site infection can be patient related (eg, age, comorbid disease, nutritional status) or procedure related (eg, complexity, surgical technique, antibiotic prophylaxis, glycemic control).[128] Various guidelines provide recommendations on the prevention of infection at the surgical site, which include maintaining strict perioperative blood glucose control, adequate perioperative oxygenation, normothermia, normovolemia, and the use of various surgical related strategies to mitigate risk.[128 141] Although no prospective studies have yet evaluated the association between perioperative infection prevention and persistent postsurgical pain, infection control should remain a cornerstone of perioperative care.

Controversies

Discogenic spine pain

Studies have shown that over 40% of herniated discs might be infected with bacteria, with the most common organism being the anaerobic bacterium *Cutibacterium acnes*.[142] In one meta-analysis by Ganko et al of nine studies with various methodologies (one included cervical discs), seven studies included patients with radiculopathy or herniated disc and two included patients with disc degeneration. The researchers found a higher infection rate in degenerated discs than in non-degenerated discs (37.4% *v* 5.9%; odds ratio 6.077, 95% confidence interval 1.426 to 25.901).[143] However, a large subsequent case-control study (n=812 total samples) that included operated cervical and lumbar discs found no difference in infection rates between symptomatic and control discs.[144] A 2018 prospective study found a 32.5% infection rate in 80 patients who underwent single level discectomy for sciatica, with a positive association between infection and endplate signal changes, but not for the degree of disc degeneration.[145] In another prospective study of 32 patients who underwent cervical discectomy and fusion, positive cultures were found in 25% of patients and 13.6% of discs, which was higher than the positive rate in controlled muscle biopsies (12.5%).[146] In this sample, coagulase-negative *Staphylococcus* was the most common microbe.

Studies have sought to evaluate the efficacy of antibiotic treatment for discogenic pain. In a review by Gilligan et al, two of four observational studies and two of three randomized controlled trials (n=413) reported benefit.[142] In the randomized trials, the two positive studies treated patients with Modic type 1 endplate changes for 100 days with amoxicillin-clavulanic acid and reported benefit at one year or end of treatment,[147 148] while the negative study treated patients with Modic type 1 and type 2 changes with only amoxicillin for 3 months and reported no meaningful benefit at one year.[149] Collectively, these results suggest that a small percentage of patients with infection-associated disc pathology might benefit from antibiotic treatment, but the heterogeneity of spine pain and lack of antibiotic penetrance could hinder results.

Inflammatory bowel disease

Inflammatory bowel disease includes Crohn's disease, which can affect any part of the gastrointestinal tract, and ulcerative colitis, which is limited to the colon. Evidence suggests that a subset of patients with inflammatory bowel disease develops symptoms secondary to an autoimmune response that targets natural gut microbiota or fails to control invasive commensal or pathogenic organisms.[150 151] In a computational analysis of a dataset from people with inflammatory bowel disease, Hassouneh et al found 34 bacterial species with concentrations at least twofold higher than that of control samples, and eight species that were less than half as abundant.[152] That many of these bacteria are implicated in immune modulation and inflammation suggests the relation between microbes and immune system impairment might be bidirectional.

Numerous studies have established higher prevalence rates of organisms (such as *Mycobacterium avium* subspecies *paratuberculosis*, adherent invasive *E coli*, *Campylobacter* species, *Clostridium difficile*, and cytomegalovirus) in patients with inflammatory bowel disease than in control patients, with minimal differences in disease stage or type of inflammatory bowel disease. Other research, including a meta-analysis examining 58 studies with various designs, found a protective effect for *Helicobacter pylori*.[153] One mechanism by which microbes can cause inflammatory bowel disease is via dysregulation of pattern recognition receptors, which include toll-like receptors and C type lectin receptors.[154]

The clinical pain presentation of inflammatory bowel disease varies according to phenotype. Abdominal pain, typically described as crampy and colicky, affects about 60% of patients, and is more common in Crohn's disease. Crohn's disease affects the entire gastrointestinal tract, so painful oral ulcers can occur, with a prevalence of around 30%.[155] Tenesmus might occur in both Crohn's disease and ulcerative colitis but is more common in the ulcerative colitis. Rheumatological manifestations affect up to 30% of patients with inflammatory bowel disease and are more common in Crohn's disease, with one meta-analysis of 71 observational studies finding an average prevalence of 13% for peripheral arthritis, 10% for sacroiliitis, 3% for ankylosing spondylitis, and lower rates for enthesitis and dactylitis.[156] Other painful manifestations might include cholangitis and hepatitis, ocular involvement, carditis, and dermatological involvement, in which the cumulative prevalence is up to 30%.[157]

The treatment of pain in inflammatory bowel disease depends on presentation. Antidepressants and opioids should be considered for flares of visceral pain, although chronic opioid use could paradoxically worsen abdominal pain. Given the high co-prevalence rates of depression, anxiety, and other psychiatric illnesses, psychotherapy can be considered.[158] Systematic reviews have found evidence for antibiotics in both Crohn's disease and ulcerative colitis, but paradoxically, the use of antibiotics in childhood could increase the risk for future inflammatory bowel disease.[159 160] Immunomodulatory drugs such as azathioprine, methotrexate, and tumor necrosis factor alpha inhibitors have shown effectiveness.[161]

Myalgic encephalomyelitis or chronic fatigue syndrome

Myalgic encephalitis or chronic fatigue syndrome is a poorly understood clinical condition characterized by post-exertional malaise lasting at least six months, associated with variable symptoms of neurological, immune, endocrine, or autonomic dysfunction.[20 162 163] The diagnosis is controversial, with no universally accepted diagnostic criteria.[164] The term "chronic fatigue syndrome" was originally proposed as an alternative to "chronic Epstein-Barr syndrome" to describe the symptom complex of chronic fatigue presenting with other (often painful) symptoms, including sore throat, lymph node pain and tenderness, headache, myalgia, and arthralgias.[165] Myalgic encephalomyelitis refers to a specific neuro-immunological condition, and has been suggested to be clinically distinct from chronic fatigue syndrome,[166] but most practitioners use the two terms synonymously or in combination.[163] Although painful symptoms were prominent in earlier case definitions of chronic fatigue syndrome,[165 167] more recent clinical diagnostic criteria have de-emphasized pain, which is not required for diagnosis.[20 168] Nevertheless, pain remains a common symptom in patients with myalgic encephalitis or chronic fatigue syndrome, and many nociplastic pain conditions (eg, fibromyalgia, temporomandibular disorder, irritable bowel syndrome, migraine) are comorbidities.[162]

No single cause has been identified for myalgic encephalitis or chronic fatigue syndrome, but immunological, psychological, neurobiological, neuroendocrine, genetic or epigenetic, circulatory, and infectious cause are the most commonly proposed categories, with viral infections implicated in up to 50% of cases in some studies.[17 169 170] In some instances, categories can overlap, for example, infectious diseases leading to autoimmune mechanisms. Myalgic encephalitis or chronic fatigue syndrome often presents sporadically, but outbreaks do occur, often in association with viral-like illnesses, suggesting infection as a possible trigger.[17] Various epidemiological studies have associated the disorder with Epstein-Barr virus, cytomegalovirus, human herpes viruses 6 or 8, parvovirus B19, enteroviruses, lentivirus, and bacteria such as mycoplasma, *Borrelia* species, and *Coxiella burnetii*.[17] Covid-19 infection has been associated with the development of prolonged symptoms similar to those found in myalgic encephalitis or chronic fatigue syndrome.[171]

Infection can trigger an autoreactive process in susceptible individuals, leading to autoimmune responses against energy metabolic processes in the brain and muscle.[170] Cytokine signatures have also been causally linked to illness severity of myalgic encephalitis or chronic fatigue syndrome,[172] and infection both inside and outside the brain could cause increased production of proinflammatory cytokines, leading to immune mediated dysfunction of the nervous system and energy metabolism.[173] Given these proposed relations, use of antiviral and immunomodulatory drugs has been suggested to treat the disorder, but such use is off-label.[174] Antiviral drugs such as acyclovir, valacyclovir, and rintatolimod appear to have limited efficacy in treating myalgic encephalitis or chronic fatigue syndrome and can be considered in patients who are seropositive for specific viruses, but evidence is limited by flawed study design and conflicting results.[175] Immunomodulatory drugs including corticosteroids, cyclophosphamide, and rituximab have failed to show broad benefit in patients with myalgic encephalitis or chronic fatigue syndrome.[175 176] These studies highlight the heterogeneous nature of the disorder and emphasize the importance of developing multimodal, precision medicine approaches to treatment.[175 176]

Effects of antimicrobial treatment on chronic pain

Chronic pain after infection could be due to numerous causes, so mixed results from studies evaluating antimicrobial treatment are not surprising. Conceptually, whereas antimicrobial treatment should alleviate pain from active inflammatory processes, it should have minimal effects on chronic pain resulting from central sensitization, irrevocable tissue (eg, arthropathy, vasculitis) or nerve injury, or ongoing immune reactions in the absence of detectable pathogen levels (table 3).

Psychological implications of infection and chronic pain

Patients with infection can experience biological, psychological, and social stressors that trigger or exacerbate acute pain, leading to chronic pain.[5] Psychological factors such as anxiety, depression, and adverse life events are risk factors for the development of chronic pain after infections.[177–180] In turn, pain could contribute to the development of mental health comorbidities, yielding a bidirectional association.[181 182]

Low psychological wellbeing before or during an infection is a risk factor for intestinal disorders after infection, such as irritable bowel syndrome and functional dyspepsia.[178–180 183 184] Stress, anxiety, and depression during an episode of acute enteritis, as well as negative life events prior to infection, could be associated with a higher risk of developing irritable bowel syndrome.[177 179 183 184] In patients with HIV associated polyneuropathy, mental health is a risk factor for neuropathic pain.[185 186] Patients with concurrent depression experience painful HIV neuropathy more frequently than patients without depression, and depressive symptoms are more severe in patients

Table 3 | Reviews of antibiotic treatment for pain conditions

Study and year	Study type	Patient population and disorder	Results	Comments
Ford et al, 2018[195]	Meta-analysis of randomized placebo controlled trials	Nine studies of 2845 patients with irritable bowel syndrome	All studies favored antibiotics compared with placebo, with three study falling just below the threshold for statistical significance	Seven studies evaluated the minimally absorbed antibiotic rifaximin, with two others evaluating ciprofloxacin and neomycin, both of which were positive. When four rifaximin studies with low risk of bias were evaluated separately, results favored antibiotics (Risk Ratio 0.87; 95% confidence interval 0.82 to 0.93).
Anothaisintawee et al, 2011[196]	Systematic review and network meta-analysis of randomized placebocontrolled trials	Three studies of 215 patients with chronic prostatitis or pelvic pain syndrome	In the network meta-analysis that included 14 studies, reduction in pain compared with placebo: Pooled risk ratio −4.4 (95% confidence interval −7.0 to −1.9) for antibiotics, −5.7 (−7.8 to −3.6) for α blockers plus antibiotics	Antibiotics plus α blockers more effective than other treatments evaluated but direct comparison based on only one study[197]; duration of treatment 6-12 weeks; antibiotics studied included ciprofloxacin, levofloxacin, and tetracycline
Wanis et al, 2017[198]	Meta- analysis of randomized controlled trials	Five studies of 337 patients with acute postsurgical pain after hemorrhoidectomy	Patients who received metronidazole had lower reported pain scores on postoperative days 1 (Standardized mean difference −0.87 (Standard error0.44); 95% confidence interval −1.73 to −0.015; P=0.046; n=4) and 4 (−1.43 (0.71); −2.83 to −0.037; P=0.044; n=3).	Two studies compared metronidazole with usual care (not blinded or placebo controlled); no significant difference was seen when the largest study with high risk of bias was excluded; longest follow-up was 14 days
Andraws et al, 2005[199]	Meta-analysis of randomized placebo controlled trials evaluating antichlamydial antibiotics	11 studies of 19 217 patients with coronary artery disease	Pooled rate of unstable angina 9.2% in antibiotic group *v* 9.6% in placebo group (odds ratio 0.91; 95% confidence interval 0.76 to 1.07; P=0.25); no significant differences in myocardial infarction or mortality rates	All studies except one (fluoroquinolone) evaluated macrolide antibiotics. Follow-up ranged from six months to four years. Subgroup analysis of patients with antichlamydial titers (three trials, n=4548 patients) also found no significant differences
Gilligan et al, 2021[142]	Narrative review	Eight studies, of which three were placebo controlled (413 patients in controlled trials had chronic low back pain and vertebral endplate signal changes)	Two of four observational studies and two of three controlled trials were positive; herniated and degenerated discs contain a low bacterial burden that could be below detection threshold and samples are prone to contamination; almost 50% of degenerated discs were infected, mostly with *Cutibacterium Acnes*	Two positive controlled studies enrolled patients with only Modic type 1 endplate signal changes and treated patients with amoxicillin-clavulanic acid, while the negative controlled study enrolled patients with Modic type 1 and 2 changes and treated patients with amoxicillin; all studies treated patients for between 90 and 100 days; both positive controlled studies showed a significant reduction in disability and pain; a subset of patients could benefit from oral antibiotic treatment but this hypothesis requires further investigation
Norton et al, 2017[200]	Systematic review	15 studies, including only one randomized study comparing effectiveness of two antibiotics (n=29), in patients with inflammatory bowel disease[201]	In the one randomized study,[201] metronidazole and ciprofloxacin both reduced abdominal symptoms (84% response rate for bloating, 47% for abdominal pain) with no difference between either antibiotic	Small bowel bacterial overgrowth present in 29 of 145 patients with Crohn's disease, with baseline abdominal pain present in 48%; no difference in response rates between metronidazole and ciprofloxacin given for 10 days; glucose breath tests returned to normal in 27 of 29 patients after treatment
Swedish Council on Health Technology Assessment, 2007[202]	Systematic review based primarily on randomized controlled trials and systematic literature reviews published between 1999 and 2005	Functional dyspepsia	Antibiotic treatment that eradicates *Helicobacter pylori* offers mild relief of functional dyspepsia symptoms (evidence grade 3), but most patients with functional dyspepsia are not infected with *H pylori* and do not benefit (evidence grade 2).	Highlights that functional dyspepsia is a disorder (not disease) with an unknown cause; results consistent with the study group's previous report in 2000 concluding that drug treatment yields very limited benefits

with painful HIV neuropathy than in patients with non-painful neuropathy.[185]

Post-infectious chronic pain can lead to psychological and social consequences such as anxiety, depression, and poor mental health.[187] For example, in one cross sectional study, half of patients with SARS experienced persistent psychological symptoms, despite few having a history of psychiatric illness, with the most common diagnoses being post-traumatic stress disorder and depression.[187] In one prospective study, the presence of depression at one month after covid-19 infection predicted persistent pain at three months.[188]

Because chronic pain, fatigue, sleep disorders, and cognitive difficulties are concurrent in post-infectious syndromes, it can be difficult to infer cause and effect, and these relationships are probably interdependent. One consistent finding across studies is a clear association between chronic pain after infection and poorer quality of life.[180–182]

Emerging studies

Further research is needed regarding the precise mechanisms by which infections can lead to chronic pain, and whether any of these processes might be therapeutic targets. However, a lack of ongoing studies answers these questions. Between the International Standard Randomised Controlled Trial Number and ClinicalTrials.gov databases, only four ongoing clinical trials pertain to infection and chronic pain. Two trials are observational, with one aiming to identify risk factors for the development of chronic pain after covid-19 infection (NCT04883216), and the other assessing whether covid-19 infection is associated with glycomic or glycan profile changes that might predispose individuals to chronic pain (NCT04788433). The two remaining trials focus on specific interventions. One randomized controlled trial is assessing whether tai chi or health coaching can improve analgesia and quality of life in patients with chronic HIV associated pain (NCT05055596), and one open label prospective trial is assessing whether oral valacyclovir can improve pain and quality of life in patients with Epstein-Barr virus who have interstitial cystitis or bladder pain syndrome (NCT05094414). The NCT05094414 study is the only one among these four that aims to elucidate a specific cause of chronic pain (Epstein-Barr virus) along with a corresponding treatment (valacyclovir). Given the global pervasiveness of chronic pain secondary to infections and its potentially debilitating effects on individuals and communities, this topic deserves greater attention.

QUESTIONS FOR FUTURE RESEARCH

- ⇒ Are there any biomarkers or phenotypes that can identify people with infection who are at higher risk for developing chronic pain, and what steps can be taken to prevent acute pain transitioning into chronic pain?
- ⇒ Can any safe and efficient interventions be given pre-emptively before common infections in patients at high risk for long term adverse consequences including chronic pain?
- ⇒ Does infection independently cause chronic pain, accelerate or accentuate the natural course of nociception (eg, unmask an ongoing process), or exacerbate psychological processes (eg, depression, anxiety) that predispose patients with acute injury to develop chronic pain? How can these related processes be distinguished?
- ⇒ What role do genetics and socioeconomic factors have in the persistence of pain after infection?
- ⇒ Does vaccination or early and aggressive treatment alter the natural course of long term sequelae, including pain after infection?

PATIENT INVOLVEMENT

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Conclusions

Chronic pain is an under-recognized result of infection and might take many forms including nociceptive, neuropathic, and nociplastic pain. Chronic pain can complicate infection by many mechanisms, including direct microbe invasion, immunological processes, treatment toxicity, and psychological triggers. For most chronic pain conditions that develop after infection, treatment is empirical, with antimicrobial agents providing minimal benefit in the absence of evidence for persistent infection. Similar to preventing the transition from acute to chronic pain for other causes, early treatment through a biopsychosocial framework could prevent chronic pain syndromes after infection, although more research is necessary.

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Funding Funded in part by a grant from MIRROR, Uniformed Services University of the Health Sciences, US Department of Defence (grant HU00011920011). The sponsor did not have a role in study design or performance, or analysis or interpretation of data.

Competing interests We have read and understood the BMJ policy on declaration of interests and declare the following interests: SPC has undertaken consultant work for Releviate, SPR Therapeutics, Avanos, Persica, and Scilex; and conducted institutional research funded by Scilex and Avanos.

Provenance and peer review Commissioned; externally peer reviewed.

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