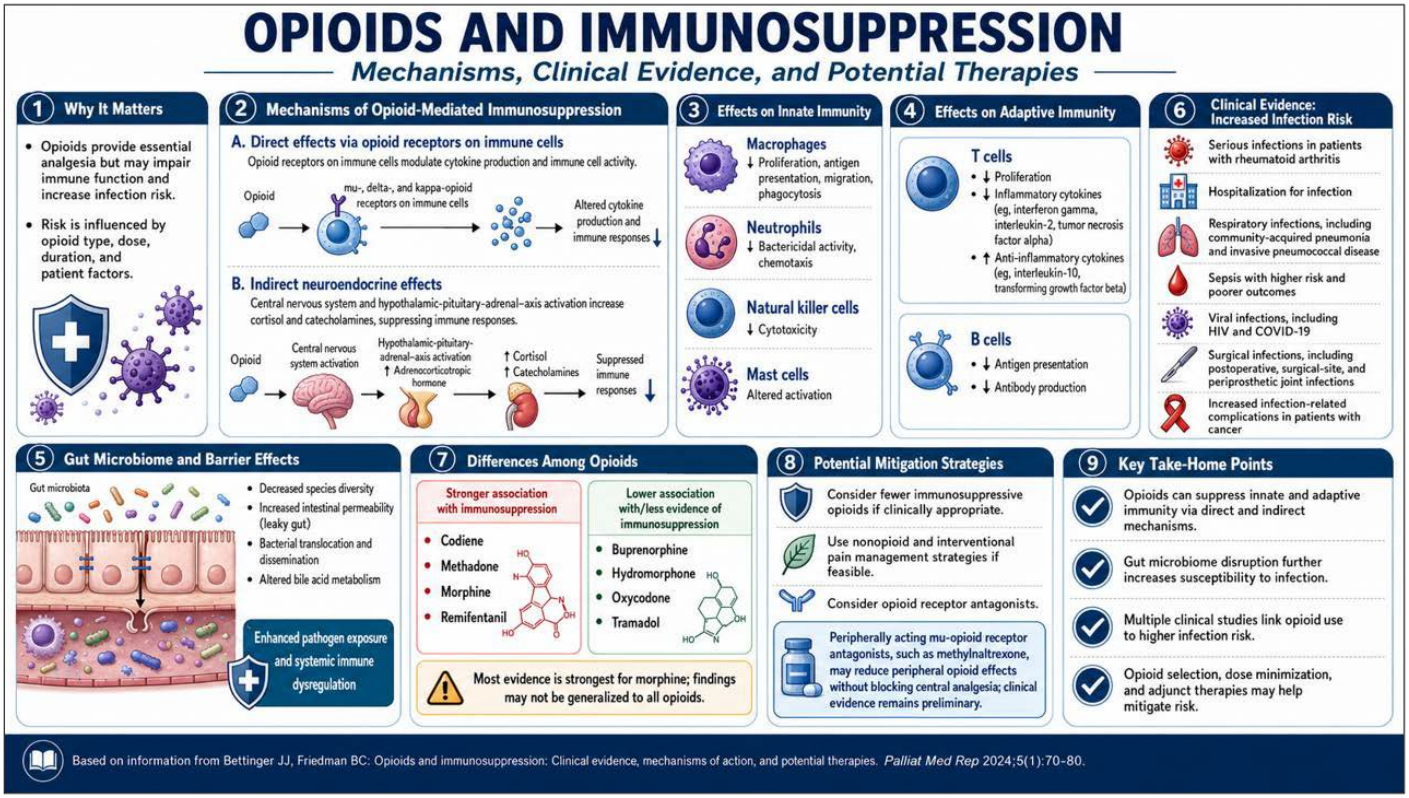

Introduction

Opioids are an important component of multimodal management for moderate to severe pain, including malignant pain, nonmalignant chronic pain, perioperative pain, and postoperative pain. The analgesic effects of opioids primarily are mediated via mu-opioid receptors; however, kappa- and delta-opioid receptors also contribute to opioid pharmacology. In addition to expected opioid-related adverse effects, such as constipation, sedation, nausea, pruritus, respiratory depression, tolerance, dependence, and hyperalgesia, opioids may impair immune function and increase susceptibility to infection.

Opioid-mediated immunosuppression is clinically important because many patients who require opioids already are medically vulnerable. This includes patients undergoing surgical treatment, patients with cancer, patients with chronic inflammatory disease, patients with HIV, patients with advanced illness, and patients undergoing long-term opioid therapy. The degree of infection risk appears to vary based on opioid type, opioid dose, opioid therapy duration, patient population, and underlying comorbidities.

The key clinical challenge is not to avoid opioids categorically but to recognize opioid-related immune effects as one component of risk assessment. In select patients, this may influence opioid selection, dose minimization, opioid therapy duration, infection surveillance, vaccination optimization, perioperative planning, and use of nonopioid or interventional pain management strategies if feasible.

Mechanisms of Opioid-Mediated Immunosuppression

Opioid receptors are expressed not only in the central nervous system and the gastrointestinal tract but also on immune cells, including neutrophils, macrophages, T cells, B cells, and natural killer cells. Therefore, opioids may influence immune function via direct receptor-mediated effects on immune cells and indirect neuroendocrine pathways.

Direct immune effects occur when opioids interact with opioid receptors on immune cells, altering cytokine production, immune-cell migration, phagocytosis, antigen presentation, and cytotoxicity. Indirect effects occur via opioid activation of central nervous system pathways and the hypothalamic-pituitary-adrenal axis, with downstream release of corticosteroids and catecholamines that may suppress immune responses.

Table 1: Major Mechanistic Pathways of Opioid-Mediated Immunosuppression

Mechanistic Pathway	Core Effect	Clinical Relevance
Direct immune-cell receptor activation	Opioids interact with receptors on immune cells.	Alters cytokine release, migration, phagocytosis, cytotoxicity, and antigen presentation
CNS and HPA-axis activation	Increased corticosteroids and stress-hormone signaling	Suppresses immune-cell activity and inflammatory responses
TLR crosstalk	Opioid receptor activity may alter TLR-4 and NFκB signaling.	May dampen innate immune activation and inflammatory signaling
Gut microbiome disruption	Reduced microbial diversity and impaired barrier function	May promote bacterial translocation, systemic inflammation, and infection susceptibility
Opioid-induced constipation	Slowed intestinal transit alters gut microbiota.	May worsen dysbiosis and reinforce gut-barrier dysfunction

CNS = central nervous system, HPA = hypothalamic-pituitary-adrenal, NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells, TLR = toll-like receptor.

Effects on Innate Immunity

Innate immunity provides the first line of defense against pathogens. Opioids, especially morphine, can impair multiple components of innate immune function.

Macrophages demonstrate reduced proliferation, recruitment, migration, phagocytosis, antigen presentation, and bactericidal activity. These changes may be partly mediated via toll-like receptor crosstalk and altered nuclear factor kappa-light-chain-enhancer of activated B cells signaling. Neutrophils may show impaired migration, reduced interleukin (IL)-8 signaling, and reduced superoxide production, limiting bactericidal activity. Dendritic-cell antigen presentation may be impaired via reduced IL-23 production. Natural killer-cell cytotoxicity is reduced, at least in part, via central mu-opioid receptor-mediated effects. Mast-cell activation also may be altered, contributing to increased intestinal permeability.

Table 2: Opioid Effects on Innate Immune Cells

Immune Cell Type	Opioid-Associated Effect	Potential Clinical Consequence
Macrophages	Reduced proliferation, recruitment, migration, phagocytosis, antigen presentation, and bactericidal activity	Impaired pathogen clearance and reduced innate immune defense
Neutrophils	Reduced migration, impaired IL-8 signaling, reduced superoxide production	Decreased bacterial killing and impaired acute inflammatory response
Dendritic cells	Reduced IL-23 production and impaired antigen presentation	Weakened bridge between innate and adaptive immunity
Natural killer cells	Reduced cytotoxicity	Impaired defense against virally infected cells and tumor surveillance
Mast cells	Altered activation and increased intestinal permeability	Increased gut barrier vulnerability and possible infection risk

IL = interleukin.

Effects on Adaptive Immunity

The effects of opioids on adaptive immunity are complex and may be direct or indirect. Morphine may reduce T-cell viability, proliferation, helper T-cell function, and cluster of differentiation 4/cluster of differentiation 8 populations. It also may reduce production of proinflammatory cytokines, such as IL-1 beta, IL-2, tumor necrosis factor alpha, and interferon gamma, while increasing anti-inflammatory cytokines, such as IL-10 and transforming growth factor beta. Morphine also may shift helper T-cell differentiation toward the T helper 2 lineage.

The effects of opioids on B cells are less extensively characterized but appear to be clinically relevant. Morphine may reduce major histocompatibility complex class II expression on B cells, impair antigen presentation, and reduce antibody production. Some of these changes may occur indirectly via reduced macrophage and T-cell support; however, direct humoral immune suppression also has been described.

Table 3: Opioid Effects on Adaptive Immunity

Immune Component	Opioid-Associated Effect	Potential Clinical Consequence
T cells	Reduced viability, proliferation, helper T-cell function, and CD4/CD8 populations	Impaired cellular immunity
Cytokine signaling	Reduced IL-1β, IL-2, TNF-α, and IFN-γ; increased IL-10 and TGF-β.	Shift toward anti-inflammatory and less pathogen-responsive state
Helper T-cell differentiation	Shift toward Th2 lineage	Altered immune balance and reduced inflammatory defense
B cells	Reduced MHC-II expression, antigen presentation, proliferation, and antibody production	Impaired humoral immunity and antigen-specific response

CD = cluster of differentiation, IFN = interferon, IL = interleukin, MHC-II = major histocompatibility complex class II, TGF = transforming growth factor, Th = T helper, TNF = tumor necrosis factor.

Gut Microbiome, Barrier Function, and Infection Susceptibility

The gut microbiome plays a central role in colonization resistance, epithelial barrier function, antimicrobial metabolite production, and systemic immune signaling. Opioids may disrupt this system via direct and indirect mechanisms.

Morphine may reduce bacterial species diversity, increase intestinal permeability, promote bacterial translocation to mesenteric lymph nodes and the liver, alter bile acid metabolism, and dysregulate immune responses. Clinical patient populations that receive opioid agonists have lower microbial diversity than patients not receiving opioid agonists. Patients with chronic opioid exposure also may have reduced beneficial short-chain fatty acid-producing bacteria, worse endotoxemia, and increased inflammatory cytokine signaling.

Opioid-induced constipation may further contribute to dysbiosis. Slowed intestinal transit is associated with microbiome changes, and altered microbiota may exacerbate constipation, creating a feed-forward loop of dysmotility, dysbiosis, barrier impairment, and systemic immune activation.

Table 4: Gut-Mediated Opioid Effects Relevant to Immunosuppression

Gut-Related Change	Mechanism	Clinical Implication
Reduced microbial diversity	Altered gut ecology	Reduced colonization resistance
Increased intestinal permeability	Barrier compromise and mucosal disruption	Greater risk of bacterial translocation
Bacterial dissemination	Translocation to lymph nodes, liver, or systemic circulation	Potential contribution to systemic inflammation or infection
Altered bile acid metabolism	Microbial and metabolic dysregulation	May affect mucosal defense and inflammatory balance
Constipation-associated dysbiosis	Slowed transit changes microbiota	May worsen barrier dysfunction and immune dysregulation

Clinical Evidence Linking Opioids to Increased Infection Risk

Although clinical evidence largely is observational, multiple studies across different patient populations have associated opioid use with increased infection risk. Serious infections, pneumonia, invasive pneumococcal disease, sepsis, viral infections, surgical-site infections, periprosthetic joint infections, and infection-related complications in patients with cancer have been evaluated.

Among patients with rheumatoid arthritis, serious infections requiring hospitalization more frequently occur during periods of current opioid use than during periods of nonuse. In patients in whom long-acting opioids are initiated, infection-related hospitalization is higher during current opioid use than during past opioid use and is highest during the first 30 days after opioid initiation.

Respiratory infections are a major area of concern. In older adults, current opioid use is associated with increased risk of community-acquired pneumonia compared with nonuse. Opioid use also is associated with increased risk of invasive pneumococcal disease. Among individuals living with HIV, prescribed opioid use is associated with community-acquired pneumonia, even after excluding patients with an opioid use disorder.

Table 5: Clinical Infection Signals Associated With Opioid Use

Clinical Setting	Reported Association
Rheumatoid arthritis	Increased serious infection during periods of opioid use
Long-acting opioid initiation	Increased hospitalization for infection, especially early after initiation of opioids
Community-acquired pneumonia	Increased risk in older adults and patients with HIV
Invasive pneumococcal disease	Increased risk among patients currently receiving opioids
Sepsis	Mixed evidence; some studies report higher mortality or higher infection burden.
Viral infection	Preclinical and limited clinical evidence involving HIV, herpes simplex virus, COVID-19, and other viruses
Surgical-site infection	Increased risk after multiple surgical procedures
Periprosthetic joint infection	Increased risk associated with preoperative and postoperative opioid use
Cancer-related infection	Evidence is mixed and confounded by disease severity, opioid dose, and treatment context.

Surgical and Orthopaedic Infection Relevance

The surgical literature is particularly relevant for orthopaedic and perioperative physicians. Multiple observational studies have reported increased infection rates in patients administered opioids before or after total joint arthroplasty. Preoperative opioid use is associated with increased risk of periprosthetic joint infection after total knee or hip arthroplasty. Opioid exposure also is associated with increased risk of periprosthetic joint infection after total hip arthroplasty.

Postoperative opioid exposure also may be relevant. A dose-dependent relationship exists between postoperative opioid use and infectious complications after total joint arthroplasty, with higher opioid exposure associated with a higher adjusted odds ratio of infection. Opioid-associated infection risk also has been reported after ventral and incisional hernia repair, left ventricular assist device support, and multilevel lumbar spine fusion.

These data do not prove that opioids directly cause surgical infections because opioid use also may reflect greater pain, greater tissue injury, more complex surgery, comorbidity, or poorer baseline health. Regardless, the consistency of these associations supports opioid stewardship as part of infection-risk mitigation.

Table 6: Practical Surgical Considerations Related to Opioids

Clinical Domain	Application
Preoperative risk assessment	Identify chronic opioid exposure as a possible marker of increased infection risk.
Opioid stewardship	Use the lowest effective opioid dose and avoid unnecessary prolonged opioid exposure.
Multimodal analgesia	Incorporate nonopioid medications and regional/interventional strategies, if appropriate.
Perioperative optimization	Address nutrition, glycemic control, smoking, immune compromise, and infection sources.
Postoperative monitoring	Maintain vigilance for wound complications in patients exposed to opioids who have a higher risk.
Patient counseling	Discuss opioid risks beyond sedation, constipation, and dependence, if clinically relevant.

Cancer and Palliative Care Considerations

Often, opioids are essential in patients with cancer pain and patients undergoing palliative care, in whom pain relief, function, comfort, and quality of life remain main priorities. Many patients with advanced cancer require opioids for pain management. This makes infection-risk interpretation especially difficult because malignancy, cachexia, chemotherapy, neutropenia, poor nutrition, indwelling devices, hospitalization, advanced disease, and immunosuppressive therapy may independently increase infection risk.

Some studies have suggested higher infection rates with the use of morphine compared with oxycodone in patients with cancer pain, whereas other studies have reported no substantial difference between specific opioids. Infection risk also may increase with higher daily morphine milligram equivalents rather than with a specific opioid; however, a higher opioid dose also may reflect more advanced illness, more severe pain, or greater systemic disease burden.

The practical approach with regard to opioids for patients with cancer and patients undergoing palliative care should be individualized. Opioids should not be withheld if clinically indicated for serious pain; however, clinicians should consider opioid type, opioid dose, opioid duration, infection surveillance, bowel management, and nonopioid adjuncts if feasible.

Differences Among Opioids

Opioids do not appear to have equivalent immunosuppressive potential. The degree of immune impairment may vary by opioid structure, receptor affinity, receptor signaling profile, dose, and duration of exposure.

Opioids more consistently associated with immunosuppression include codeine, methadone, morphine, and remifentanil. Based on available studies, buprenorphine, hydromorphone, oxycodone, and tramadol appear to have less immunosuppressive activity; however, these distinctions should be interpreted cautiously. Most mechanistic evidence is related to morphine, and the immune effects of morphine may not be generalized to all opioids.

Several mechanisms may explain differential immunosuppression. Structural differences may influence lymphocyte proliferation, IL-2 production, and natural killer-cell activity. Differential receptor affinity may play a role; however, affinity alone does not explain all findings. Differences in beta-arrestin recruitment, receptor conformational change, and downstream signaling also may contribute. For example, buprenorphine appears less strongly immunosuppressive despite high receptor affinity, possibly because of distinct signaling behavior.

Table 7: Opioid-Specific Immunosuppressive Potential[a]

Stronger Association With Immunosuppression	Lower Association With/Less Evidence of Immunosuppression
Codeine	Buprenorphine
Methadone	Hydromorphone
Morphine	Oxycodone
Remifentanil	Tramadol

[a]These categories reflect available preclinical and clinical evidence rather than definitive comparative safety rankings. Patient context, opioid dose, opioid duration, administration route, comorbid illness, and confounding by indication remain important considerations.

Potential Therapies and Mitigation Strategies

Because opioids are clinically necessary for many patients, mitigation strategies should focus on reducing avoidable immune-related risk while preserving analgesia and quality of life.

One proposed strategy involves the use of opioid receptor antagonists. In experimental models, nonselective opioid antagonists, such as naltrexone and naloxone, can block opioid-mediated immune effects, including inhibition of natural killer-cell activity, antibody production, macrophage phagocytosis, chemotaxis, and pathogen-related mortality; however, they also block central opioid analgesia and, therefore, are not appropriate for patients who require ongoing opioid analgesic therapy.

Peripherally acting mu-opioid receptor antagonists (PAMORAs) are of interest because they block peripheral mu-opioid receptors without crossing the blood-brain barrier. Currently, methylnaltrexone, naldemedine, and naloxegol are prescribed for opioid-induced constipation. The theoretic advantage of PAMORAs is that they may counteract peripheral opioid effects, including gut dysmotility and peripheral immune effects, while preserving central analgesia; however, clinical evidence that PAMORAs reverse opioid-induced immunosuppression remains preliminary.

Methylnaltrexone has shown intriguing signals in post hoc analyses, including improved survival in some patient populations; however, causality and mechanism remain uncertain. Improved outcomes may be related to bowel function, immune modulation, anticancer effects, or other unmeasured factors. Currently, PAMORAs should not be considered an established immunoprotective therapy; however, they represent an important area for future study.

Table 8: Risk-Mitigation Strategies for Opioids

Strategy	Rationale	Clinical Caveat
Use opioids only if clinically indicated.	Reduces unnecessary exposure	Pain must be adequately managed.
Use the lowest effective dose and the shortest appropriate duration.	May reduce dose- and duration-related immune risk	Must balance analgesia, function, and quality of life
Consider opioids that are less immunosuppressive, if appropriate.	Some opioids appear to have less immune effects.	Evidence is incomplete and patient-specific factors predominate.
Use multimodal analgesia.	Reduces reliance on opioids	Requires individualized planning and monitoring
Optimize bowel management.	May reduce constipation-associated dysbiosis	Does not directly prove immune-risk reduction
Consider PAMORAs for opioid-induced constipation.	Blocks peripheral mu-opioid receptors without reversing analgesia	Immunoprotective benefit remains investigational.
Address modifiable infection risks.	Vaccination, glycemic control, wound care, nutrition, smoking cessation	Especially important in surgical, cancer, and chronic disease populations

PAMORA = peripherally acting mu-opioid receptor antagonist.

Clinical Pearls

Opioid-mediated immunosuppression should be considered a potential systemic effect of opioid therapy, particularly in patients who are medically vulnerable and patients who require long-term, high-dose, or perioperative opioid exposure. The strongest mechanistic evidence is for morphine; however, clinical infection signals have been reported across multiple patient populations exposed to opioids.

Infection risk likely is multifactorial. Opioid exposure may interact with disease severity, immobility, respiratory depression, constipation, gut dysbiosis, immune-cell dysfunction, comorbid illness, and social or behavioral risk factors. Therefore, opioid use should be viewed as a possible biologic contributor to infection risk and a marker of clinical vulnerability.

For surgeons and perioperative physicians, chronic opioid use should prompt attention to infection prevention, multimodal analgesia, and postoperative surveillance. For oncologists and palliative care clinicians, the goal is not opioid avoidance but thoughtful opioid selection, dose stewardship, bowel management, and infection vigilance while preserving comfort and quality of life.

Key Take-Home Points

- Opioids can suppress innate and adaptive immune responses via direct immune-cell effects and indirect central nervous system and hypothalamic-pituitary-adrenal axis mechanisms.
- The strongest mechanistic evidence for immunosuppression is for morphine; however, not all opioids appear to have equal immune effects.
- Opioid exposure may impair macrophage, neutrophil, dendritic-cell, natural killer-cell, T-cell, and B-cell function.
- Gut microbiome disruption, increased intestinal permeability, and opioid-induced constipation may contribute to systemic immune dysregulation.
- Observational studies link opioid use to increased rates of serious infection, pneumonia, invasive pneumococcal disease, surgical-site infection, periprosthetic joint infection, and select viral complications.
- Opioid considerations are especially relevant in surgical and orthopaedic populations because preoperative and postoperative opioid exposure is associated with infectious complications.
- Opioid stewardship, multimodal analgesia, infection-risk optimization, and individualized opioid selection may help reduce risk.
- PAMORAs are a biologically plausible strategy for mitigating peripheral opioid effects; however, their role in preventing opioid-related immunosuppression remains investigational.

Conclusion

Opioid-mediated immunosuppression is an important and underrecognized clinical problem. Mechanistic evidence demonstrates that opioids can impair innate immunity, adaptive immunity, cytokine signaling, gut microbiome composition, and intestinal barrier function. Clinical studies, although mostly observational, consistently suggest increased infection risk across several opioid-exposed patient populations, including patients with inflammatory disease, patients with respiratory infection, patients who undergo surgery, patients who undergo arthroplasty, and select patients with cancer.

The available evidence does not support indiscriminate opioid avoidance, particularly if opioids are required for severe pain management or palliative care. Instead, the literature supports more precise opioid stewardship. Physicians should consider opioid type, opioid dose, opioid duration, patient vulnerability, infection risk, bowel function, and opportunities for multimodal or interventional pain management. Future prospective studies are necessary to clarify causality, identify opioids associated with the greatest immune risk, determine patient populations that are most vulnerable, and assess whether peripheral opioid antagonists or other strategies can reduce infection risk without compromising analgesia.

Reference

Bettinger JJ, Friedman BC: Opioids and immunosuppression: Clinical evidence, mechanisms of action, and potential therapies. *Palliat Med Rep* 2024;5(1):70-80.

Educational Content Disclosure

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