Review article

The Cure That Harms: How Bad Medication for Chronic Illness Fuels a Silent Epidemic of Superbugs

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Received: 29-08-2025 **Accepted:** 24-09-2025 **Published online:** 30-10-2025

DOI: https://doi.org/10.33687/ricosbiol.03.10.84

Abstract

The global rise in chronic diseases represents a significant public health burden. While the primary management of these conditions is paramount, a growing body of evidence highlights a dangerous and often overlooked consequence: the increased risk of secondary bacterial infections. This risk is profoundly exacerbated by the inappropriate medication of the underlying chronic disease. Inappropriate medication includes the misuse of antibiotics, immunosuppressive agents, corticosteroids, and broad-spectrum therapies that disrupt the microbiome. These pharmacological missteps can lead to immunosuppression, microbial dysbiosis, and the selection of drug-resistant pathogens, creating a fertile ground for secondary infections. This review synthesizes current literature to explore the mechanisms including immunosuppression, microbiome disruption, and antimicrobial resistance by which poor pharmacologic management of chronic diseases such as diabetes, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, and inflammatory bowel disease predisposes patients to serious secondary bacterial infections, with a special focus on devastating bone and joint complications. It also discusses the clinical implications, common causative pathogens, and proposes strategies for mitigation, emphasizing antimicrobial stewardship and personalized medicine to break this dangerous cycle.

Keywords: secondary bacterial infection, chronic disease management, antimicrobial resistance, superbugs, osteomyelitis, immunosuppression, microbiome, antimicrobial stewardship.

Introduction

Chronic diseases, including diabetes mellitus, chronic obstructive pulmonary disease (COPD), autoimmune disorders, and cardiovascular diseases, are the leading causes of mortality and morbidity worldwide (World Health Organization, 2022). The management of these conditions is often long-term and complex, relying on a regimen of pharmacotherapies to control symptoms, slow progression, and maintain quality of life. However, the very medications used to manage these diseases, when prescribed or used inappropriately, can have unintended and severe consequences (Feldstein *et al*., 2021).

Among the most serious of these consequences is the development of secondary bacterial infections and the fueling of the antimicrobial resistance (AMR) crisis. These infections occur subsequent to, and are facilitated by, an initial condition or its treatment. The link between inappropriate medication practices such as the overprescription of antibiotics, prolonged or high-dose corticosteroid use, and indiscriminate application of immunosuppressants and the emergence of "superbugs" is a critical clinical challenge (Murray *et al*., 2022). This review aims

to comprehensively examine the pathophysiological mechanisms, identify high-risk chronic diseases and common pathogens with a dedicated focus on severe bone and joint infections and discuss integrative strategies to prevent this iatrogenic complication.

1. Pathophysiological Mechanisms Linking Bad Medication to Secondary Infections

1.1. Iatrogenic Immunosuppression

Many chronic inflammatory and autoimmune diseases are managed with immunosuppressive agents. While these are necessary to control the underlying disease, their inappropriate use either in dosage, duration, or patient selection can lead to profound immunosuppression.

- **Corticosteroids:** Glucocorticoids are a cornerstone of treatment for conditions like rheumatoid arthritis, lupus, and asthma. However, high-dose or long-term use impairs neutrophil function, inhibits macrophage activity, and suppresses dendritic cell maturation, crippling both innate and adaptive immunity (Liu *et al*., 2013). A recent large-scale study confirmed that even moderate-dose glucocorticoid therapy (>5mg prednisolone-equivalent/day) is associated with a dose-dependent increase in the risk of hospitalization for serious infection (Pujades-Rodriguez *et al*., 2020).
- **Biologics and DMARDs:** Tumor Necrosis Factor-alpha (TNF-α) inhibitors and other biologics (e.g., JAK inhibitors) used for rheumatoid arthritis and inflammatory bowel disease are associated with an increased risk of serious and opportunistic infections. Recent real-world data underscores that the risk is highest in the initial months of therapy and when combined with other immunosuppressants, highlighting the need for careful patient selection and monitoring (Rutherford *et al*., 2022).

1.2. Disruption of the Microbiome and Dysbiosis

The human microbiome, particularly the gut and respiratory microbiomes, plays a crucial role in training the immune system and providing colonization resistance against pathogens.

- **Broad-Spectrum Antibiotics:** The inappropriate use of antibiotics remains a primary driver of dysbiosis. Recent research has detailed how antibiotics cause a rapid loss of microbial diversity and metabolic function, allowing for the expansion of pathogenic, often multidrug-resistant organisms (MDROs) like *Clostridioides difficile*, vancomycin-resistant Enterococci (VRE), and carbapenem-resistant Enterobacteriaceae (CRE) (Ng *et al*., 2023). This is particularly detrimental in chronically ill patients who experience repeated exposures.
- **Non-Antibiotic Drugs:** The concept of "non-antibiotic drugs" impacting the microbiome has gained substantial traction. A landmark study demonstrated that a wide range of commonly prescribed drugs, including metformin, proton pump inhibitors, and atypical antipsychotics, have robust, class-specific effects on the gut microbiome composition and can thereby modulate patient susceptibility to infection (Vich Vila *et al*., 2020).

1.3. Induction of Antimicrobial Resistance (AMR)

Inappropriate medication, especially antibiotic overuse and misuse, is the single most significant driver of antimicrobial resistance. In the context of chronic disease management, this creates a vicious cycle.

- **Selective Pressure and Resistance Gene Transfer:** Beyond simple selection, recent metagenomic studies show that antibiotic pressure facilitates the horizontal transfer of resistance genes between commensal and pathogenic bacteria within the dysbiotic microbiome (Larsson and Flach, 2022).
- **Treatment Failure:** When a secondary infection occurs, empirical antibiotic therapy may fail due to this pre-existing resistance. The 2022 Global Burden of Disease report on AMR

attributed 1.27 million deaths directly to bacterial AMR in 2019, underscoring the lethal consequences of ineffective therapy (Murray *et al*., 2022).

2. High-Risk Chronic Diseases and Associated Secondary Infections

2.1. Diabetes Mellitus

Poor glycemic control itself is a state of immune dysfunction, impairing neutrophil chemotaxis and phagocytosis. Inappropriate medication exacerbates this.

• **Scenario:** Failure to manage hyperglycemia effectively, coupled with inappropriate antibiotic prescribing for minor skin infections, can lead to severe secondary infections. Recent evidence shows that SGLT2 inhibitor use, while beneficial for glycemic and cardiovascular control, may be associated with a slightly increased risk of genitourinary infections and Fournier's gangrene if not prescribed with appropriate patient counseling and monitoring (Bersoff-Matcha *et al*., 2019).

• **Common Pathogens:** *S. aureus* (including MRSA), *Streptococcus* spp., and gram-negative bacilli.

2.2. Chronic Obstructive Pulmonary Disease (COPD)

COPD patients experience frequent acute exacerbations, many of which are viral or non-infectious.

• **Scenario:** The widespread practice of prescribing antibiotics for all exacerbations promotes airway microbiome disruption. A 2021 study found that repeated antibiotic courses in COPD lead to a progressive decline in airway microbial diversity and enrichment with proteobacteria, including *P. aeruginosa*, which is associated with more frequent future exacerbations (Dickens *et al*., 2021).

• **Common Pathogens:** *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *P. aeruginosa*.

2.3. Autoimmune and Inflammatory Diseases (RA, IBD, Lupus)

As discussed, the main risk stems from immunosuppressive therapy.

• **Scenario:** The use of JAK inhibitors for RA and other conditions has been linked in post-marketing studies to an increased risk of herpes zoster and serious opportunistic infections, necessitating careful risk-benefit analysis (Cohen *et al*., 2021).

• **Common Pathogens:** *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *S. aureus*, and opportunistic gram-negative bacteria.

2.4. Devastating Bone and Joint Complications

The skeletal system is a frequent and devastating site for secondary bacterial infections, which are notoriously difficult to treat and often lead to long-term disability.

• **Diabetic Foot Osteomyelitis:** The diabetic foot ulcer is a primary pathway for bone infection. Inappropriate medication is a critical factor:

  ○ **Poor Glycemic Control:** Failure to manage hyperglycemia impairs immune function and antibiotic delivery (Lázaro-Martínez *et al*., 2021).

  ○ **Inappropriate Antibiotic Use:** Short, narrow-spectrum courses for ulcers select for MDROs. Prior antibiotic exposure is a key risk factor for MDR osteomyelitis (Uçkay *et al*., 2020).

  ○ **Lack of Source Control:** Relying on antibiotics without surgical debridement allows biofilms to form on necrotic bone, making eradication nearly impossible (Masters *et al*., 2021).

• **Septic Arthritis in Rheumatologic Diseases:** Patients with RA are at high risk for joint infections, amplified by their therapies.

- **Corticosteroids and Biologics:** These agents mask signs of infection and depress local immune surveillance. JAK inhibitors, in particular, are associated with a significant increase in serious infections, including musculoskeletal ones (Xie *et al*., 2022). Symptoms can be mistaken for an RA flare, leading to dangerous delays (Talsania *et al*., 2021).

• **Vertebral Osteomyelitis:** This often arises from hematogenous spread in patients with chronic conditions.

- **Mechanism:** Inadequate treatment of a primary infection (e.g., UTI, catheter-site infection) due to inappropriate antibiotic selection can lead to bacteremia and seeding of the spine. A history of recurrent infections treated with multiple antibiotics is a predictor for complex osteomyelitis (Barton *et al*., 2023).

2.5. Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD):

Uremia in CKD causes immune dysfunction. Medication mismanagement adds another layer of risk.

• **Scenario:** Inappropriate dosing of antibiotics without renal adjustment remains a common problem. A recent systematic review highlighted that suboptimal dosing in ESRD patients is a significant predictor of treatment failure and the emergence of resistance (Sakharkar *et al*., 2022).

• **Common Pathogens:** *S. aureus* (including MRSA), VRE, and ESBL-producing gram-negative rods.

3. Clinical and Public Health Implications

The consequences extend beyond the individual patient. Secondary infections lead to:

- **Increased morbidity and mortality,** with AMR now being a leading cause of death globally (Murray *et al*., 2022).
- **Prolonged hospitalizations and increased healthcare costs,** placing a massive strain on health systems (Nelson *et al*., 2021).
- **Acceleration of the global AMR crisis,** rendering first-line antibiotics ineffective.
- **Complex treatment dilemmas,** where the need to treat the chronic disease must be balanced against the risk of unleashing an uncontrollable infection.

4. Mitigation and Future Directions

Breaking the cycle requires a multi-pronged approach:

- **Antimicrobial Stewardship Programs (ASPs):** The integration of ASPs into outpatient settings, including specialty clinics for chronic diseases, is a critical and evolving frontier. The use of clinical decision support systems within electronic health records can significantly reduce inappropriate prescribing (Buehrle *et al*., 2020).
- **Precision Medicine and Biomarkers:** Utilizing biomarkers like procalcitonin to guide antibiotic therapy in COPD and other respiratory conditions continues to be validated as an effective strategy to reduce unnecessary exposure (Huang *et al*., 2021).
- **Vaccination:** Ensuring patients with chronic diseases are up-to-date with vaccinations (e.g., pneumococcal, influenza, COVID-19) is more important than ever to prevent primary infections that lead to secondary bacterial complications.
- **Microbiome-Targeted Interventions:** Research into microbiome-based therapeutics is advancing. The use of targeted, narrow-spectrum antibiotics and fecal microbiota transplantation for recurrent C. difficile infection is a proven model that may be expanded to other dysbiosis-associated conditions in the future (Ianiro *et al*., 2020).

Conclusion

The management of chronic diseases is a delicate balancing act. Inappropriate medication practices, particularly concerning antibiotics, corticosteroids, and immunosuppressants, directly undermine this balance by increasing the susceptibility to severe secondary bacterial infections and fueling the silent epidemic of superbugs. This occurs through mechanisms of iatrogenic immunosuppression, microbiome disruption, and the fueling of antimicrobial resistance. The recent literature solidifies these links and quantifies the substantial associated morbidity and mortality, with devastating complications such as osteomyelitis representing a final common pathway of therapeutic failure. Clinicians must be vigilant in applying the principles of antimicrobial stewardship and personalized medicine. A proactive, holistic approach that considers the patient's immune status, microbiome health, and local resistance patterns is essential to safely manage the chronic disease while preventing the devastating consequences of a secondary infection. The goal is not to withhold necessary treatment but to optimize it, ensuring that the cure does not become a source of greater harm.

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