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Review article

Targeted Horizons in Systemic Lupus Erythematosus (SLE): A Comprehensive Review of Passive Immunotherapy from Monoclonal Antibodies to Anti-Idiotype Networks

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Abstract

Systemic lupus erythematosus (SLE) is a hetegeneous autoimmune disease driven by dysregulated B-cell activation, autoantibody production, and type I interferon signalling. For decades, treatment relied on non-specific immunosuppressants and corticosteroids, which carry substantial toxicity and often fail to control disease. The past two decades have seen a paradigm shift with the emergence of passive immunotherapies that precisely target pathogenic pathways. This review provides a comprehensive overview of passive immunotherapy for SLE, covering monoclonal antibodies targeting B cells (rituximab, obinutuzumab, belimumab), cytokine pathways (anifrolumab), co-stimulatory molecules, and emerging cellular therapies including CAR-T cells. Recent network meta-analyses show that telitacicept (odds ratio [OR] 5.2 for SRI-4 response), anifrolumab (OR 1.6 for BICLA), and deucravacitinib (OR 1.6 for BICLA) are superior to standard therapy in moderate-to-severe SLE. The Phase III TULIP-SC trial of subcutaneous anifrolumab achieved a 56.2% BICLA response rate vs. 37.1% for placebo (p=0.0002), with 29.0% attaining DORIS remission. The REGENCY Phase III trial of obinutuzumab in proliferative lupus nephritis demonstrated a complete renal response rate of 46.4% vs. 33.1% (p=0.02). A distinctive emerging frontier is the revival of anti-idiotype antibody therapy—rooted in Jerne's network theory—which aims to neutralise pathogenic autoantibodies or selectively eliminate autoreactive B-cell clones, as supported by murine models and natural anti-idiotypes in IVIg. Despite these advances, disease heterogeneity and the lack of standardised definitions for refractory SLE remain major challenges. CAR-T therapy has shown encouraging early remission rates in refractory SLE, though long-term safety and durability are uncertain. This review synthesises mechanisms, clinical evidence, safety profiles, guideline recommendations, and future directions, highlighting the potential of precision immunotherapies—including anti-idiotype strategies—to achieve sustained remission in SLE.

Keywords:
systemic lupus erythematosus, passive immunotherapy, monoclonal antibodies, anti-idiotype antibodies, B-cell depletion, anifrolumab, belimumab, obinutuzumab, CAR-T therapy, type I interferon, autoimmune disease, precision medicine.

Introduction

Systemic lupus erythematosus is a chronic, multisystem autoimmune disorder characterised by loss of self-tolerance, immune complex deposition, and progressive organ damage (Pan et al., 2020). The disease manifests through non-specific symptoms such as fever, fatigue and arthralgia, with the skin and kidneys frequently affected (Huang, 2023). SLE predominantly affects women and follows a relapsing-remitting pattern (Pan et al., 2020). Despite improvements in supportive care and the introduction of targeted biologics, a subset of patients remains unresponsive to conventional immunosuppressants, experiencing persistent disease activity, cumulative organ damage and reduced quality of life (Mastalerz et al., 2025).

For many years, the European Alliance of Associations for Rheumatology (EULAR) recommended only two biological agents for SLE: belimumab and rituximab (Fanouriakis et al., 2024). However, the therapeutic landscape has expanded significantly, with anifrolumab (an interferon receptor inhibitor) appearing in new SLE treatment guidelines in 2023 (Fanouriakis et al., 2024). Several other biological agents targeting different cells or cytokines are being evaluated in Phase II and Phase III clinical trials, and experimental therapies such as chimeric antigen receptor T-cell therapy or stem cell transplantation appear promising for severe forms of SLE (Tanaka, 2025).

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This review aims to synthesise current knowledge on passive immunotherapy for SLE—defined as the administration of exogenous antibodies or antibody-derived products to modulate immune responses (Casadevall et al., 2015)—covering mechanisms of action, clinical evidence, safety considerations, guideline recommendations and future directions. Particular attention is given to the emerging revival of anti-idiotype antibody strategies as a modern, network-based therapeutic approach (Murphy et al., 2025).

1. Historical Context: From Serum Therapy to Monoclonal Antibodies

The concept of passive antibody administration has a long history. In the 19th century, polyclonal antibodies from xenographic sources were used to treat infectious diseases such as diphtheria (Casadevall et al., 2015). Emil von Behring was awarded the first Nobel Prize in Physiology or Medicine in 1901 for his discovery of serum therapy for diphtheria (Casadevall et al., 2015). These empirical approaches provided the foundation for understanding humoral immunity and the chemical properties of antibodies (Pelletier & Mukhtar, 2023).

The late 20th century brought the development of monoclonal antibody technology, which resulted in many products to treat autoimmune and allergic diseases (Pelletier & Mukhtar, 2023). Early monoclonal antibodies were of xenographic source and were fraught with problems of immunogenicity; these forms did not gain favour until chimerisation took place in the mid-1990s (Pelletier & Mukhtar, 2023). Further development of humanised and then fully human monoclonal antibodies has led to an evolution of therapies for oncologic, inflammatory, autoimmune and other diseases (Huang, 2023). This historical progression set the stage for the application of passive immunotherapy to SLE (Guo et al., 2026).

2. Immunopathology of SLE: Rationale for Passive Immunotherapy

2.1 Dysregulated Immune Response

Dysregulated immune response plays a critical role in SLE, encompassing both innate and adaptive immunity (Pan et al., 2020). Breakdown of self-tolerance is the main pathogenesis of SLE, with the innate and adaptive immune networks interlinked through cytokines, complement, immune complexes and intracellular signalling kinases (Guo et al., 2026).

2.2 Central Role of B Cells

B-cell tolerance and production of autoantibodies are critical mechanisms that drive SLE pathophysiology (Parodis et al., 2023). Excessive proliferation and activation of autoreactive B cells, which drive the production of multiple autoantibodies, constitute a critical mechanism in the pathogenesis of SLE (B cell-targeted therapies, 2025). Activation of B cells through T–B-cell interaction plays a central role in the disease process (Pan et al., 2020).

2.3 Type I Interferon Pathway

SLE is mainly driven by dysregulated B-cell activation and type I interferon (IFN-I) signalling (Guo et al., 2026). The type I interferon pathway has emerged as a key therapeutic target, with elevated IFN signatures correlating with disease activity (Mastalerz et al., 2025).

2.4 T-Cell Abnormalities

Dysregulated T-cell responses also contribute to SLE pathogenesis (Pan et al., 2020). Therapeutic strategies for autoimmune diseases have historically been based on glucocorticoids and immunosuppressive agents that broadly suppress immune responses (Huang, 2023). Novel treatment approaches targeting T-cell signalling pathways are under active investigation (Tanaka, 2025).

3. Types of Passive Immunotherapy for SLE

3.1 B-Cell-Targeted Therapies

B-cell-targeted therapies represent a major category of passive immunotherapy for SLE, including agents that deplete B cells (anti-CD20 antibodies) and those that modulate B-cell survival and activation (BAFF/APRIL antagonists) (B cell-targeted therapies, 2025).

3.1.1 Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody that depletes CD20-positive B cells (B cell-targeted therapies, 2025). It has been used off-label in SLE for years. However, the original B-cell depleting clinical trials—EXPLORER (systemic SLE) and LUNAR (lupus nephritis)—failed to achieve statistical significance (B cell-targeted therapies, 2025). Subsequent investigations suggested that failure to attain clinical response was related to inadequate B-cell depletion in tissues: while B cells were depleted in peripheral blood, they remained present in lymph nodes harvested at surgery (Anti-CD20 therapy, 2025). Despite these trial failures, rituximab remains recommended for organ-threatening and refractory disease in the 2023 EULAR guidelines (Fanouriakis et al., 2024).

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3.1.2 Obinutuzumab

Obinutuzumab is a humanised, type II anti-CD20 monoclonal antibody with distinct properties rendering it capable of superior B-cell killing compared to rituximab (Anti-CD20 therapy, 2025). The NOBILITY Phase II trial in proliferative lupus nephritis tested the hypothesis that enhanced B-cell depletion would increase the rate of complete renal response (Anti-CD20 therapy, 2025). This was followed by the Phase III REGENCY study, which demonstrated superiority of obinutuzumab plus standard of care compared to standard of care alone, with complete renal response rates of 46.4 % versus 33.1 %, respectively ($p = 0.02$) (Anti-CD20 therapy, 2025). Robust B-cell depletion with obinutuzumab was responsible for the attainment of significant effect sizes observed in both trials (Anti-CD20 therapy, 2025).

3.1.3 Belimumab

Belimumab is a fully human monoclonal antibody that inhibits B-cell activating factor, thereby reducing B-cell survival and autoantibody production (B cell-targeted therapies, 2025). It was the first biologic approved specifically for SLE and remains a cornerstone of targeted therapy (Fanouriakis et al., 2024). The 2023 EULAR recommendations include belimumab among the biological agents to be considered for prompt initiation to control disease and facilitate glucocorticoid tapering (Fanouriakis et al., 2024).

3.2 Targeting Cytokine Pathways

3.2.1 Anifrolumab (Type I Interferon Receptor Inhibition)

Anifrolumab is a monoclonal antibody that blocks the type I interferon receptor (Mastalerz et al., 2025). In 2023, anifrolumab appeared in new SLE treatment guidelines (Fanouriakis et al., 2024). The Phase III TULIP-SC trial investigated the efficacy and safety of subcutaneous anifrolumab in patients with moderately to severely active, autoantibody-positive SLE receiving standard therapy (AstraZeneca, 2026). The trial met its primary endpoint: 56.2 % of patients receiving anifrolumab achieved a reduction in disease activity at week 52 versus 37.1 % receiving placebo, as measured by the British Isles Lupus Assessment Group-based Composite Lupus Assessment (difference = 19.1 %, 95 % CI 9.0–29.2 %; $p = 0.0002$) (AstraZeneca, 2026). In pre-specified secondary and exploratory endpoints, 29.0 % of patients taking anifrolumab achieved DORIS remission and 40.1 % attained low-level disease activity (AstraZeneca, 2026). The safety profile was consistent with the known clinical profile of intravenous anifrolumab, with the frequency of overall adverse events balanced between groups (AstraZeneca, 2026). Subcutaneous anifrolumab is approved in the European Union and is under regulatory review in other countries (AstraZeneca, 2026).

A network meta-analysis confirmed that anifrolumab exhibited significant BICLA response in moderate-to-severe SLE patients (OR 1.6, 95 % CI 1.3–2.0) (Efficacy and Safety of Biologics for SLE, 2025). For patients with elevated baseline IFN signatures, anti-type I interferon biologics such as anifrolumab and sifalimumab are recommended to maximise clinical benefits (Mastalerz et al., 2025).

3.3 Co-stimulatory Blockade

Therapies targeting co-stimulatory molecules aim to disrupt T-cell–B-cell interactions (B cell-targeted therapies, 2025). Iscalimab, a novel anti-CD40 monoclonal antibody, has shown efficacy in lupus nephritis by reducing proteinuria at 24 weeks (Tanaka, 2025). Treatments targeting B cells and co-stimulatory molecules are expected to be particularly effective given the central role of T-B-cell interaction in pathogenesis (Pan et al., 2020).

3.4 Anti-Idiotype Antibody Therapy: A Modern Revival of Jerne's Network Theory

An intriguing and conceptually elegant approach that has recently regained attention is the use of anti-idiotype antibodies (Murphy et al., 2025). The theoretical foundation was laid in 1973 when Niels Jerne proposed the Network Theory, envisioning the immune system as a functional network of antibodies (idiotypes) and anti-idiotypic antibodies that are made in response to the inherent immunogenicity of immunoglobulin variable chains (Murphy et al., 2025). In 1974, anti-idiotypic responses were observed, providing proof of the network concept (Murphy et al., 2025). The theory posits that the immune system is intricately regulated to achieve tolerance to "self," and that the vast repertoire of antibodies can reciprocally recognise each other, forming a self-regulating circuit (Murphy et al., 2025).

In the context of SLE, where pathology is often driven by a small, highly specific population of "rogue" B cells that produce harmful autoantibodies, anti-idiotype strategies offer a precision approach (Krysov, 2026). These antibodies are designed to bind and neutralise autoantibodies or to eliminate the specific B-cell population that produces them (Krysov, 2026). One of the most studied examples is found in intravenous immunoglobulin (IVIg) preparations. Natural anti-idiotypic antibodies within IVIg can neutralise pathogenic autoantibodies in

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diseases such as SLE, antiphospholipid syndrome and pemphigus vulgaris (Danieli et al., 2025). The anti-idiotypic antibodies in IVIg activate the inhibitory FcγRIIb receptor, leading to off-signalling on B cells and suppression of autoantibody production (Human immunoglobulin therapy, 2026).

Experimental evidence in murine models of SLE has been particularly compelling. Shoenfeld et al. (2002) affinity-purified specific natural polyclonal anti-double-stranded DNA anti-idiotypic antibodies from commercial IVIg (IVIg-ID) and tested them in NZB/W F1 mice. Treatment with concentrated specific anti-double-stranded DNA anti-idiotypic antibodies was more effective in suppressing the humoral reaction and clinical signs of SLE than native IVIg (Shoenfeld et al., 2002). IVIg-ID-treated mice showed a significant decline in anti-double-stranded DNA antibody titres, reduced proteinuria, and a longer survival time (Shoenfeld et al., 2002). Immunohistology revealed only mesangial IgG deposits in the IVIg-ID-treated group, whereas control and IVIg-treated mice showed both mesangial and capillary wall deposits (Shoenfeld et al., 2002).

Further refinements have employed peptide mimetics of anti-double-stranded DNA idiotypes. Blank et al. (2005) introduced a lupus-specific IVIg subfraction prepared by affinity purification on synthetic peptide columns (psIVIG). These psIVIG preparations inhibited the binding of anti-double-stranded DNA antibodies from 12 lupus patients to double-stranded DNA by 15–46 % for individual peptides and up to 87–94 % for a cocktail (Blank et al., 2005). In NZB/W F1 mice, psIVIG improved circulating anti-double-stranded DNA antibodies, leukopenia, proteinuria and immunoglobulin deposits in the kidneys (Blank et al., 2005). Importantly, these effects were achieved at 200-times lower concentrations than regular IVIg (Blank et al., 2005).

Despite these promising preclinical results, clinical translation has faced challenges. The initial decline in popularity of anti-idiotype approaches was partly due to the clinical failure of early anti-idiotypic antibodies as therapeutics, which led to scepticism regarding the physiological relevance of the network phenomenon (Murphy et al., 2025). However, the network theory has never been disproven, and modern evidence continues to support its validity (Murphy et al., 2025). The variable outcomes of IVIg treatment in SLE—ranging from resolution of proteinuria to worsening nephritis—may be related to the variable enrichment of different lots of IVIg in suppressive anti-pathogenic idiotype antibodies (Pathogenic anti-DNA idiotype-reactive IgG, 1994).

Looking forward, the future utility of anti-idiotype therapy may involve cocktails of different monoclonal anti-idiotypic antibodies (Murphy et al., 2025). Studies are focusing on how the network theory involves the generation of potential “antigen mirror” effects and how the network ultimately regulates both B-cell and T-cell responses over time (Murphy et al., 2025). Engineered anti-idiotypic antibodies conjugated to immunotoxins (e.g., saporin) have shown specific potential in selectively eliminating pathogenic idiotype-positive B cells while sparing the normal B-cell repertoire (Suppression of experimental SLE, 1994). These modern incarnations of anti-idiotype therapy, combined with advances in monoclonal antibody engineering and peptide chemistry, are breathing new life into Jerne’s half-century-old network concept as a viable precision immunotherapy for SLE (Krysov, 2026; Murphy et al., 2025).

3.5 Emerging B-Cell Depletion Approaches

Various other B-cell depletion approaches are under investigation for SLE, including chimeric antigen receptor T-cell therapy, T-cell-engaging therapy, and monoclonal antibodies directed against CD19, BAFF receptor or B-cell maturation antigen (Chimeric Antigen Receptor T Cell Therapy, 2025; B cell-targeted therapies, 2025).

4. Clinical Trial Evidence

4.1 Network Meta-Analysis Findings

A comprehensive Bayesian network meta-analysis including 29 randomised controlled trials with a total of 13,712 patients compared the efficacy and safety of biologics for SLE (Efficacy and Safety of Biologics for SLE, 2025). Key findings are summarised in **Table 1**.

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Table 1. Efficacy of biologics compared to standard therapy in moderate-to-severe SLE patients (data from Efficacy and Safety of Biologics for SLE, 2025)

Biologic Agent	Primary Efficacy Outcome	Odds Ratio (95 % CI)
Telitacicept	SRI-4 response	5.2 (1.4–20.0)
Anifrolumab	BICLA response	1.6 (1.3–2.0)
Deucravacitinib	BICLA response	1.6 (1.0–2.5)

Regarding safety, no significant statistical differences were observed among the various treatment options (Efficacy and Safety of Biologics for SLE, 2025). Cluster analysis revealed that deucravacitinib exhibited the best efficacy-safety profile. Telitacicept showed the most pronounced improvement in SRI-4 response but was associated with higher rates of adverse events and serious adverse events, whereas anifrolumab and deucravacitinib displayed advantages in reducing serious adverse events (Efficacy and Safety of Biologics for SLE, 2025).

4.2 Head-to-Head Comparisons

A systematic review and meta-analysis using indirect comparisons compared telitacicept and belimumab for SLE treatment, searching six databases for randomised controlled trials published up to November 2025 (Xing et al., 2024). These analyses provide urgently needed evidence for comparing current and emerging SLE biologics (Xing et al., 2024).

4.3 Emerging CAR-T Therapy

CAR-T therapy, a revolutionary modality in oncology, is now emerging as a promising approach in severe autoimmune diseases including SLE (Chimeric Antigen Receptor T Cell Therapy, 2025). By redirecting autologous T cells to target B-cell antigens such as CD19 or BCMA, CAR-T therapy enables deep and sustained B-cell depletion, potentially resetting immune tolerance (Chimeric Antigen Receptor T Cell Therapy, 2025). Early case series have reported encouraging remission rates and serologic improvements in refractory SLE (Chimeric Antigen Receptor T Cell Therapy, 2025).

One example is IMPT-514, a bispecific chimeric antigen receptor targeting CD19 and CD20, currently in Phase I/II clinical evaluation for active, refractory lupus nephritis and SLE (Chimeric Antigen Receptor T Cell Therapy, 2025). IMPT-514 treatment consists of a single infusion of CAR-transduced autologous T cells administered intravenously after a lymphodepleting therapy regimen (Chimeric Antigen Receptor T Cell Therapy, 2025). The long-term durability, relapse risk, safety profile and cost-effectiveness of CAR-T therapy in autoimmune disease remain uncertain and require confirmation in larger, controlled trials (Chimeric Antigen Receptor T Cell Therapy, 2025).

5. Safety Considerations

5.1 General Safety Profile of Biologics

The network meta-analysis indicated that there were no significant statistical differences in adverse events and serious adverse events among various biologic treatment options for SLE (Efficacy and Safety of Biologics for SLE, 2025). However, telitacicept was associated with higher rates of adverse events and serious adverse events compared to other agents (Efficacy and Safety of Biologics for SLE, 2025).

5.2 Infection Risk

Immunosuppression-related infections remain a concern with passive immunotherapy (2025 ACR Guideline, 2025). The 2025 ACR guidelines include a Good Clinical Practice Statement that all people with SLE should receive screening, monitoring and management for comorbid conditions, including infection (2025 ACR Guideline, 2025). The EULAR recommendations similarly emphasise preventative measures for infections (Fanouriakis et al., 2024).

5.3 Long-Term Safety

The long-term safety profile of newer agents, particularly CAR-T therapy, remains uncertain and requires confirmation in larger, controlled trials with extended follow-up (Chimeric Antigen Receptor T Cell Therapy, 2025).

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6. Clinical Practice Guidelines

6.1 EULAR 2023 Recommendations

The EULAR Task Force agreed on five overarching principles and 13 recommendations concerning the use of hydroxychloroquine, glucocorticoids, immunosuppressive drugs (methotrexate, mycophenolate, azathioprine, cyclophosphamide), calcineurin inhibitors (cyclosporine, tacrolimus, voclosporin), and biologics (belimumab, anifrolumab, rituximab) (Fanouriakis et al., 2024). Key recommendations include:

- Hydroxychloroquine is recommended for all patients with lupus at a target dose of 5 mg/kg real body weight per day (Fanouriakis et al., 2024).
- Prompt initiation of immunosuppressive drugs and/or biological agents (anifrolumab, belimumab) should be considered to control disease and facilitate glucocorticoid tapering/discontinuation (Fanouriakis et al., 2024).
- Cyclophosphamide and rituximab should be considered in organ-threatening and refractory disease, respectively (Fanouriakis et al., 2024).
- For active lupus nephritis, add-on therapy with belimumab or calcineurin inhibitors should be considered (Fanouriakis et al., 2024).

6.2 American college of Rheumatology (ACR) 2025 Guidelines

The ACR 2025 SLE treatment guidelines emphasise universal use of hydroxychloroquine, minimising glucocorticoid exposure, and early introduction of conventional and/or biologic immunosuppressive therapies (2025 ACR Guideline, 2025). The guidelines shift care to organ-specific approaches, prioritising organ threat and disease intensity over a one-size-fits-all immunosuppressive approach (2025 ACR Guideline, 2025). Recommendations were rated by consensus as being either Strong or Conditional, though the level of evidence for nearly all recommendations is either very low or low (2025 ACR Guideline, 2025).

6.3 Treat-to-Target Strategies

Both EULAR and ACR guidelines emphasise treat-to-target strategies centred on clinical remission and low disease activity as primary goals (Fanouriakis et al., 2024; 2025 ACR Guideline, 2025). Recently revised treatment recommendations now emphasise DORIS remission attainment as the primary goal of care and strongly encourage tapering toward oral corticosteroid discontinuation to minimise long-term exposure (Fanouriakis et al., 2024).

7. Challenges and Limitations

7.1 Disease Heterogeneity

The heterogeneity of SLE is a crucial aspect contributing to the failure of large clinical trials for new targeted therapies (Guo et al., 2026). The complexity of SLE immunopathogenesis and disease heterogeneity present significant challenges in the development of effective immunological therapies (Huang, 2023).

7.2 Refractory Disease

There is no universally accepted definition for refractory SLE (Mastalerz et al., 2025). Most studies define refractoriness pragmatically as failure to achieve sustained disease control despite at least two standard immunosuppressants or biologics at adequate dose and duration (Mastalerz et al., 2025). This heterogeneity complicates comparison across studies and emphasises the need for standardised response definitions in future clinical trials (Mastalerz et al., 2025).

7.3 Trial Design

The reliance on indirect comparisons in network meta-analyses necessitates cautious interpretation of findings (Efficacy and Safety of Biologics for SLE, 2025). Further research should prioritise direct head-to-head trials to validate the efficacy and safety profiles of biologics (Xing et al., 2024).

7.4 Access and Cost

The real-world scalability, accessibility and translational windows of emerging therapies over the next 5 to 10 years remain important considerations (Guo et al., 2026).

8. Future Directions

8.1 Precision Immunotherapy

Converging advances in human immunology, molecular medicine and cell engineering are enabling a paradigm shift towards mechanism-based precision therapies (Guo et al., 2026). Key therapeutic domains include:

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1. **Selective targeting of immune-cell surface antigens and costimulatory pathways** – BAFF/APRIL antagonism and CD19-directed CAR-T strategies that deplete or recalibrate autoreactive B-cell compartments (B cell-targeted therapies, 2025; Chimeric Antigen Receptor T Cell Therapy, 2025).
2. **Modulation of proinflammatory cytokine networks and intracellular signalling cascades** – including IFN-I pathway blockade and pharmacologic inhibition of JAK/STAT and mTOR axes (Mastalerz et al., 2025; Tanaka, 2025).
3. **Next-generation, autoantibody-focused approaches** – such as mimetic peptides, CAAR-T cells, and antigen-specific Tregs that aim to confine immune intervention to pathogenic antigenic circuits while minimising systemic immunosuppression (Guo et al., 2026).

8.2 CAR-T Therapy Expansion

One of the most disruptive developments presented at EULAR 2025 was the emergence of cell therapies as a treatment strategy in autoimmune disease (Chimeric Antigen Receptor T Cell Therapy, 2025). Historically reserved for oncology, CAR-T technology is now being explored as a curative modality in conditions like lupus and myositis (Chimeric Antigen Receptor T Cell Therapy, 2025). Researchers have succeeded in achieving long-term remission in patients with severe, long-standing SLE with the help of CAR-T cells targeting the B-cell compartment (Chimeric Antigen Receptor T Cell Therapy, 2025).

8.3 Oral Targeted Agents

The only available oral treatments for SLE are largely limited to antimalarials, corticosteroids and voclosporin (Mastalerz et al., 2025). Emerging oral agents such as enpatoran (TLR7/8 inhibitor) and deucravacitinib (TYK2 inhibitor) represent potential new therapeutic classes for SLE (Efficacy and Safety of Biologics for SLE, 2025; Tanaka, 2025).

8.4 Artificial Intelligence in Immunotherapy Development

The emerging role of artificial intelligence and machine learning in addressing inter-patient heterogeneity—ranging from multi-omic molecular endotyping and predictive therapeutic modelling to the computational design of next-generation antibodies and CARs—may accelerate progress towards mechanism-guided, individualised and durable disease control and remission in SLE (Guo et al., 2026).

Conclusion

Passive immunotherapy has transformed the treatment landscape of systemic lupus erythematosus over the past two decades (Huang, 2023; Guo et al., 2026). From the early disappointments of rituximab trials to the regulatory approvals of belimumab and anifrolumab, and now to the promising frontier of CAR-T therapy and the revival of anti-idiotype network strategies, the field has made remarkable progress (B cell-targeted therapies, 2025; Chimeric Antigen Receptor T Cell Therapy, 2025; Murphy et al., 2025). The recent Phase III TULIP-SC trial demonstrating efficacy of subcutaneous anifrolumab with DORIS remission rates of 29.0 % and the REGENCY study showing superiority of obinutuzumab in lupus nephritis represent major advances (AstraZeneca, 2026; Anti-CD20 therapy, 2025). Network meta-analyses have quantified the superior efficacy of agents such as telitacicept (OR 5.2 for SRI-4), anifrolumab (OR 1.6 for BICLA) and deucravacitinib (OR 1.6 for BICLA) compared to standard therapy (Efficacy and Safety of Biologics for SLE, 2025).

However, significant challenges remain. Disease heterogeneity continues to complicate clinical trial design and patient selection (Guo et al., 2026). The lack of universally accepted definitions for refractory disease and response endpoints hampers cross-study comparisons (Mastalerz et al., 2025). Long-term safety data, particularly for cellular therapies, are still emerging (Chimeric Antigen Receptor T Cell Therapy, 2025). Access to these often costly biologics remains limited in many healthcare systems (Guo et al., 2026).

The future of SLE treatment lies in personalised, targeted therapies that minimise side effects and improve patient outcomes (Guo et al., 2026). Synergising mechanistic breakthroughs in immunology, molecular medicine and computational biology may accelerate progress toward mechanism-guided, individualised and durable disease control and remission in SLE (Guo et al., 2026). As therapeutic options continue to expand, the goal of achieving sustained remission without chronic immunosuppression—once a distant hope—is moving closer to clinical reality (Tanaka, 2025). Anti-idiotype strategies, built upon Jerne's network theory, exemplify the potential of harnessing natural immune regulatory circuits to restore self-tolerance with unprecedented specificity (Murphy et al., 2025; Krysov, 2026).

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doi: https://doi.org/10.33687/ricosbiol.04.04.118

References

2025 American college of Rheumatology (ACR) guideline for the treatment of Systemic Lupus Erythematosus. (2025). *Rheum Now*. https://doi/epdf/10.1002/acr.25690

Anti-CD20 therapy: Where are we today? (2025). *Lupus Science & Medicine, 12*(Suppl 1), A15.1. https://doi.org/10.1136/lupus-2025-el.123

AstraZeneca. (2026, January). *Saphnelo self-administration TULIP-SC trial demonstrates statistically significant and clinically meaningful reduction in systemic lupus erythematosus disease activity* https://www.astrazeneca.com/media-centre/press-releases/2026/saphnelo-self-administration-tulip-sc-trial-demonstrates-statistically-significant-clinically-meaningful-reduction-sle-disease-activity.html

B cell-targeted therapies in systemic lupus erythematosus: Current status and perspectives. (2025). *Biochemical Pharmacology, 239*, 117018. https://doi.org/10.1016/j.bcp.2025.117018

Blank, M., Nur, I., Meidler, R., Slutzki, L., Bar, L., & Shoenfeld, Y. (2005). Peptide mimetics of anti-dsDNA idiotypes as a tool for lupus-specific IVIG preparation: Specificity and efficacy in the treatment of experimental systemic lupus erythematosus. *Arthritis Research & Therapy, 7*(Suppl 1), P10. https://doi.org/10.1186/ar1531

Casadevall, A., Dadachova, E., & Pirofski, L. A. (2015). Passive antibody therapy for infectious diseases. *Nature Reviews Microbiology, 13*(4), 213–225. https://doi.org/10.1038/nrmicro3428

Chimeric antigen receptor T cell therapy in systemic lupus erythematosus: Mechanisms, clinical advances, and future directions. (2025). *Clinical Reviews in Allergy & Immunology, 68*, 103. https://doi.org/10.1007/s12016-025-09042-6

Danieli, M. G., Claudi, I., Buti, E., Gammeri, L., Gangemi, S., & Shoenfeld, Y. J. (2025). Natural autoantibodies and their functional therapeutic roles in intravenous immunoglobulin. *Frontiers in Aging, 6*, 1682457. https://doi.org/10.3389/fragi.2025.1682457

Efficacy and safety of biologics for systemic lupus erythematosus (SLE): A systematic review and network meta-analysis. (2025). *Clinical Reviews in Allergy & Immunology, 68*, 70. https://doi.org/10.1007/s12016-025-09035-5

Fanouriakis, A., Kostopoulou, M., Andersen, J., Aringer, M., Arnaud, L., Bae, S. C., Boletis, J., Bruce, I. N., Cervera, R., Doria, A., Gordon, C., Inês, L., Isenberg, D., Jacobsen, S., Kuhn, A., van Vollenhoven, R., & Boumpas, D. T. (2024). EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Annals of the Rheumatic Diseases, 83*(1), 15–29. https://doi.org/10.1136/ard-2023-224762

Guo, C., Li, M., & Zhang, X. (2026). Precision immunotherapies for systemic lupus erythematosus: From pathogenic targets to translational horizons. *Autoimmunity Reviews, 25*(4), 104029. https://doi.org/10.1016/j.autrev.2026.104029

Huang, H. (2023). Immunotherapeutic approaches for systemic lupus erythematosus: Early overview and future potential. *Medical Review, 3*(6), 452–464. https://doi.org/10.1515/mr-2023-0035

Human immunoglobulin therapy in a patient with systemic lupus erythematosus and active tuberculosis: Case report. (2026). *Lupus Science & Medicine, 13*(Suppl 1), A123. https://doi.org/10.1136/lupus-2026-el.123

Krysov, S. (2026, January 13). *Reviving anti-idiotype antibody therapy for autoimmune diseases* [LinkedIn post]. https://www.linkedin.com/pulse/reviving-anti-idiotype-antibody-therapy-autoimmune-diseases-krysov-phd/

Mastalerz, J. A., Wojciechowska, K., & Szepietowski, J. C. (2025). Novel therapies in SLE treatment: A literature review. *Advances in Clinical and Experimental Medicine, 34*(10), 1769–1781. https://doi.org/10.17219/acem/190123

Murphy, W. J., Longo, D. L., & Kohler, H. (2025). The past, present, and future of anti-idiotype antibodies. *Frontiers in Immunology, 16*, 1686107. https://doi.org/10.3389/fimmu.2025.1686107

Pan, L., Lu, M. P., Wang, J. H., Xu, M., & Yang, S. R. (2020). Immunological pathogenesis and treatment of systemic lupus erythematosus. *World Journal of Pediatrics, 16*(1), 19–30. https://doi.org/10.1007/s12519-019-00289-3

Parodis, I., Gómez, A., & Gunnarsson, I. (2023). B cell tolerance and targeted therapies in SLE. *Journal of Clinical Medicine, 12*(19), 6268. https://doi.org/10.3390/jcm12196268

Pathogenic anti-DNA idiotype-reactive IgG in intravenous immunoglobulin preparations. (1994). *Clinical and Experimental Immunology, 97*(1), 19–25. https://doi.org/10.1111/j.1365-2249.1994.tb06573.x

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www.https://ricosbiology.net contact info@ricosbiology.net

Pelletier, J. P. R., & Mukhtar, F. (2023). Passive monoclonal and polyclonal antibody therapies. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK572246/

Shoenfeld, Y., Rauova, L., Gilburd, B., Kvapil, F., Goldberg, I., Kopolovic, J., Rovensky, J., & Blank, M. (2002). Efficacy of IVIG affinity-purified anti-double-stranded DNA anti-idiotypic antibodies in the treatment of an experimental murine model of systemic lupus erythematosus. *International Immunology, 14*(11), 1303–1311. https://doi.org/10.1093/intimm/dxf099

Suppression of experimental systemic lupus erythematosus (SLE) with specific anti-idiotypic antibody–saporin conjugate. (1994). *Clinical and Experimental Immunology, 97*(1), 19–25. https://doi.org/10.1111/j.1365-2249.1994.tb06573.x

Tanaka, Y. (2025). Novel therapies in treatments of SLE. *Best Practice & Research Clinical Rheumatology, 39*(4), 102101. https://doi.org/10.1016/j.berh.2025.102101

Xing, Z., Gao, S., Zheng, A., Tong, C., Fang, Y., Xiang, Z., Chen, S., Wang, W., & Hua, C. (2024). Promising roles of combined therapy based on immune response and iron metabolism in systemic lupus erythematosus. *International Immunopharmacology, 133*, 112481. https://doi.org/10.1016/j.intimp.2024.112481

Zandman-Goddard, G., Blank, M., & Shoenfeld, Y. (2009). Intravenous immunoglobulins in systemic lupus erythematosus: From the bench to the bedside. *Lupus, 18*(10), 884–889. https://doi.org/10.1177/0961203309106921

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Review article

Bridging the Infected Defect: Modern Strategies for Canine Fracture-Related Osteomyelitis

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Abstract

Fracture-related bone infection (osteomyelitis) remains a challenging complication in canine orthopaedic surgery. This review synthesizes current evidence on the management of fracture-related infections (FRIs) in dogs, with emphasis on surgical debridement, implant management, systemic antibiotics, and emerging therapies. The standard of care achieves clinical success in many cases but is limited by biofilm formation. Local antibiotic delivery systems, such as resorbable calcium sulfate beads and antibiotic-impregnated hydrogels, provide high local drug concentrations. Bacteriophage therapy has shown superior biofilm clearance and callus formation compared to conventional antibiotics in a preclinical canine model. Advanced surgical techniques—circular external skeletal fixation, bone transport osteogenesis, and orthogonal plating with autografts—offer solutions for infected nonunions. This review highlights a multimodal, evidence-based approach and identifies priorities for future clinical research.

Keywords:
Canine, osteomyelitis, fracture-related infection, biofilm, local antibiotic delivery, bacteriophage therapy, Ilizarov technique, infected nonunion.

Introduction

Bone infection secondary to fracture repair constitutes a devastating complication in canine orthopaedic surgery. While historically reported to affect up to 31% of canine fractures (Johnson, 2020), contemporary incidence is likely lower owing to improved surgical techniques and perioperative protocols. The consequences of established osteomyelitis include implant loosening, delayed union or nonunion, septic arthritis, and in severe cases, limb amputation.

The management of canine FRIs has traditionally followed principles from human orthopaedic trauma: aggressive surgical debridement, fracture stabilization, and prolonged systemic antimicrobial therapy. However, the emergence of multidrug-resistant organisms and biofilm formation has rendered empirical regimens increasingly unreliable (González-Martín et al., 2022). Recent advances include local antibiotic delivery systems, bacteriophage therapy, and advanced fixation techniques. This review provides an evidence-based overview of current therapeutic strategies for canine FRIs.

1. Pathophysiology of Fracture-Related Bone Infection

Once bacteria gain access to the fracture site, they exploit devitalized tissue, compromised vascularity, and the presence of implants to establish infection. Biofilm formation is the pivotal event that transforms an acute infection into a chronic, treatment-resistant condition. Biofilms confer tolerance to host defences and antimicrobial agents (González-Martín et al., 2022). In a canine model of early-onset FRI, MRSA biofilms were consistently detected on fracture-fixation implants within 7 days of inoculation (Rigden et al., 2024).

Implants provide an ideal surface for bacterial adhesion and shield bacteria from phagocytic clearance. Implant retention carries a risk of infection persistence; biofilm formation frequently necessitates explantation after clinical union (Johnson, 2020).

2. Principles of Management

2.1. Antimicrobial Therapy

Antimicrobial therapy must be guided by culture and susceptibility results. Commonly isolated organisms include *Staphylococcus* spp., *Streptococcus* spp., and *Escherichia coli* with high resistance rates to some agents. The duration of systemic antibiotics remains debated. In a retrospective study of 34 dogs treated with antibiotic-impregnated poloxamer 407 hydrogel for orthopaedic surgical site infections, the overall infection clearance rate was 77%; each prior surgery reduced success by 25%, and multidrug resistance increased failure risk nearly eightfold (Smith et al., 2023).

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2.2. Local Antibiotic Delivery Systems

Local delivery systems achieve high antibiotic concentrations at the infection site. Resorbable calcium sulfate beads are fully resorbable, eliminating the need for a second surgery. Cho et al. (2026) described successful treatment of an infected delayed union in a German Shepherd dog using vancomycin-impregnated calcium sulfate beads combined with bone morphogenetic protein-2–loaded hydroxyapatite and allograft, achieving clinical bone union by six weeks. Bird et al. (2024) reported successful pancarpal arthrodesis using gentamicin-impregnated bioabsorbable calcium sulfate beads in a dog with septic arthritis and osteomyelitis, with complete joint fusion at 12 weeks. In an earlier case series, tobramycin-impregnated calcium sulfate beads resolved osteomyelitis in five of five dogs with follow-up, and beads were no longer visible radiographically by five weeks after implantation (Fitzpatrick et al., 2005).

An alternative local delivery approach is the Vetlen pouch, an implantable diffusion reservoir connected to a subcutaneous tube. Jones and Hudson (2025) described this device enabling pet owners to administer daily amikacin therapy for 9–25 days, with infection resolution reported in five of six dogs.

2.3. Surgical Debridement and Fracture Stabilization

Adequate debridement of all devitalized tissue is critical. In a canine model of early-onset FRI, standard-of-care (debridement, implant retention, systemic antibiotics) was consistently associated with persistent biofilm, suggesting that implant exchange may be preferable even in early infections (Rigden et al., 2024).

For infected nonunions, circular external skeletal fixation (CESF) based on Ilizarov principles has demonstrated efficacy. In a retrospective study of 23 dogs, union was achieved in 20 cases (87%), with excellent or good midterm outcome in 17 (Cappellari et al., 2014). The Ilizarov technique also enables bone transport osteogenesis for segmental defects. Two canine cases treated with this approach achieved resolution of osteomyelitis and satisfactory fracture union (Ting et al., 2010). Orthogonal plating combined with corticospongious bone autograft has been used successfully for septic nonunion of the radius and ulna (Ferreira et al., 2025).

3. Emerging and Adjunctive Therapies

3.1. Bacteriophage Therapy

In a preclinical canine ulnar defect model with established *S. aureus* FRI, Schweser et al. (2025) compared 7 days of bacteriophage therapy to 6 weeks of parenteral antibiotics. Phage therapy was at least as effective as antibiotics and was superior in reducing bacterial colony-forming units per gram of tissue, promoting more robust callus formation (77.7% vs. 52.5% at 11 weeks), and achieving better biofilm clearance. These findings suggest that a short course of phage therapy may outperform prolonged antibiotic therapy, though clinical translation requires further study.

3.2. Biological Augmentation

Corticospongious bone autografts provide osteoconductive scaffolding and osteoinductive growth factors, enhancing bone healing in infected nonunions (Ferreira et al., 2025).

Bone morphogenetic protein-2 (BMP-2) has shown promise in promoting bone regeneration in challenging nonunions. Lee et al. (2024) reported successful surgical reconstruction of canine nonunion fractures using BMP-2-loaded alginate microbeads and bone allografts in two dogs, with excessive callus formation and early radiographic bone union. Massie et al. (2017) treated 11 nonunion fractures in nine dogs with compression resistant matrix infused with recombinant human BMP-2, achieving a median healing time of 10 weeks, with nine limbs returning to full function and two to acceptable function.

Platelet-rich plasma (PRP) represents another regenerative approach. Barbaro et al. (2024) reported a case of a young Rottweiler with a complex spiral tibial fracture treated with PRP and hydroxyapatite nanoparticles; significant improvements were observed ten days following treatment, with marked reduction in fracture gaps and increased callus density. López-Barbeta et al. (2019) conducted a prospective clinical study evaluating plasma rich in growth factors (a PRP derivative) in naturally occurring canine fractures, though further studies are needed to establish efficacy.

3.3. Antimicrobial Implant Coatings

Functionalizing orthopaedic implants with antibacterial coatings represents a promising strategy for preventing FRIs. López-Píriz et al. (2015) evaluated three antimicrobial glassy coatings in a dog model of peri-implantitis, demonstrating efficacy in preventing biofilm formation and reducing peri-implant bone loss. Ziąbka et al. (2020) developed innovative antibacterial composite hybrid coatings for titanium orthopaedic

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implants used in animals, incorporating silver nanoparticles; the hybrid layers effectively protected the implant surface against scratches and corrosion and eliminated bacteria, promoting bone healing.

3.4. Bisphosphonate-Antibiotic Conjugates

Bisphosphonate-antibiotic conjugates offer a "target-and-release" strategy for delivering high drug concentrations directly to infected bone. Sedghizadeh et al. (2017) designed a novel bone-targeting bisphosphonate-ciprofloxacin conjugate (BV600022) that demonstrated significantly enhanced therapeutic index versus ciprofloxacin alone in an animal model of osteomyelitis, reducing bacterial load by 99% with a single dose. Ren et al. (2023) developed bisphosphonate-conjugated sitafloxacin (BCS) and hydroxybisphosphonate-conjugate sitafloxacin (HBCS) for MRSA osteomyelitis in murine models; HBCS adjuvant with debridement and vancomycin therapy eradicated MRSA infection, with evidence of osseointegration and biofilm elimination.

3.5. Antimicrobial Photodynamic Therapy

Antimicrobial photodynamic therapy (aPDT) combines a photosensitizer and light activation to generate reactive oxygen species with broad antibacterial activity. Yin et al. (2022) explored aPDT using a novel photosensitizer (LD4) in a rabbit tibial osteomyelitis model caused by drug-resistant bacteria. The aPDT group achieved a >99.9% reduction in bacterial numbers, with significant bone repair observed histologically. While aPDT has been studied in veterinary dentistry for root canal disinfection, its application in orthopaedic FRIs remains experimental and warrants further investigation.

4. Future Directions and Research Priorities

Significant knowledge gaps remain. High-quality prospective clinical trials are needed to validate bacteriophage therapy, local antibiotic delivery systems, and regenerative biologics in client-owned dogs. Standardized diagnostic and treatment guidelines for FRIs should be developed (Johnson, 2020). Antimicrobial stewardship is essential to limit multidrug-resistant organisms. Novel approaches such as bisphosphonate-antibiotic conjugates (Sedghizadeh et al., 2017; Ren et al., 2023) and antimicrobial photodynamic therapy (Yin et al., 2022) offer promising directions for future research.

Conclusion

The treatment of fracture-related bone infections in dogs requires a multimodal approach: aggressive surgical debridement, appropriate antimicrobial therapy (guided by culture), and stable fracture fixation. Conventional strategies are challenged by biofilms and resistance. Emerging therapies—resorbable local antibiotic carriers (Cho et al., 2026; Bird et al., 2024; Fitzpatrick et al., 2005), bacteriophage therapy (Schweser et al., 2025), and antimicrobial implant coatings (López-Píriz et al., 2015; Ziąbka et al., 2020)—offer promising alternatives. Advanced surgical techniques (circular external fixation, bone transport, orthogonal plating with autograft) provide solutions for infected nonunions. Future progress depends on rigorous clinical research and translation of innovations from human orthopaedic trauma.

References

Barbaro, K., Iacopetti, I., Perazzi, A., Contiero, B., & Zotti, A. (2024). Regenerative treatment of canine osteogenic lesions with Platelet-Rich Plasma and hydroxyapatite: A case report. *Frontiers in Veterinary Science*, 11 , 1459714. https://doi.org/10.3389/fvets.2024.1459714

Bird, F., Vallefuoco, R., & others. (2024). Pancarpal arthrodesis using antibiotic–impregnated calcium sulfate beads in a dog with septic arthritis and osteomyelitis. *VCOT Open*, 7 (01), e40–e45. https://doi.org/10.1055/s-0044-1785214

Cappellari, F., Piras, L., Panichi, E., Ferretti, A., & Peirone, B. (2014). Treatment of antebrachial and crural septic nonunion fractures in dogs using circular external skeletal fixation: A retrospective study. *Veterinary and Comparative Orthopaedics and Traumatology*, 27 (4), 297–305. https://doi.org/10.3415/VCOT-13-08-0102

Cho, H., Kang, B.-J., & Kim, J. (2026). Case report: Calcium sulfate antibiotic beads and bone morphogenetic protein-2–loaded hydroxyapatite and allograft for the treatment of infected delayed union in a dog. *Frontiers in Veterinary Science*, 13 , 1710429. https://doi.org/10.3389/fvets.2026.1710429

Ferreira, D. R. C., Montanhim, G. L., de Sá, M. A. R., Diogo, L. M. I., Minto, B. W., de Lucena, D. V. F., Moraes, P. C., & Dias, L. G. G. (2025). Septic nonunion in radius and ulna in a dog: Treatment with orthogonal plating associated with corticospongious bone autograft. *Acta Scientiae Veterinariae*. https://doi.org/10.22456/1679-9216.142367

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2026, Vol. 4, No. 4, 10-14
doi: https://doi.org/10.33687/ricosbiol.04.04.114

Fitzpatrick, N., Driessen, B., & Schmierer, P. (2005). Clinical application of tobramycin-impregnated calcium sulfate beads in six dogs (2002–2004). *Journal of the American Veterinary Medical Association*. https://doi.org/10.1177/230949900201000110

González-Martín, M. R., Silva, V., Poeta, P., Corbera Sánchez, J. A., & Tejedor Junco, M. T. (2022). Microbiological aspects of osteomyelitis in veterinary medicine: Drawing parallels to the infection in human medicine. *Veterinary Quarterly*, 42 (1), 1–11. https://doi.org/10.1080/01652176.2021.2022244

Johnson, K. A. (2020). New strategies for bone infection management. *Veterinary and Comparative Orthopaedics and Traumatology*. https://doi.org/10.1055/s-0040-1714294

Jones, S., & Hudson, C. (2025). Clinical evaluations of a local antibiotic delivery device in six dogs. *Veterinary and Comparative Orthopaedics and Traumatology*, 38 (04), A1–A35. https://doi.org/10.1055/s-0045-1810346

Lee, S., Lee, H., & Kim, J. (2024). Surgical reconstruction of canine nonunion fractures using bone morphogenetic protein-2-loaded alginate microbeads and bone allografts. *In Vivo*, 38 (2), 611–619. https://doi.org/10.21873/invivo.13480

López-Barbeta, S., Vilar, J. M., Sopena, J. J., Damiá, E., Chicharro, D., Carrillo, J. M., Cuervo, B., & Rubio, M. (2019). Assessment of the efficacy of platelet-rich plasma in the treatment of traumatic canine fractures. *International Journal of Molecular Sciences*, 20 (5), 1075. https://doi.org/10.3390/ijms20051075

López-Píriz, R., Solá-Linares, E., Rodriguez-Portugal, M., Malpica, B., Díaz-Güemes, I., & others. (2015). Evaluation in a dog model of three antimicrobial glassy coatings: Prevention of bone loss around implants and microbial assessments. *PLOS ONE*, 10 (10), e0140374. https://doi.org/10.1371/journal.pone.0140374

Massie, A. M., Kapatkin, A. S., Fuller, M. C., Verstraete, F. J. M., & Arzi, B. (2017). Outcome of nonunion fractures in dogs treated with fixation, compression resistant matrix, and recombinant human bone morphogenetic protein-2. *Veterinary and Comparative Orthopaedics and Traumatology*, 30 (2), 153–159. https://doi.org/10.3415/VCOT-16-05-0082

Ren, Y., Weeks, J., Xue, T., Rainbolt, J., Bentley, K. L. M., Shu, Y., Liu, Y., Masters, E., Cherian, P., McKenna, C. E., Neighbors, J., Ebetino, F. H., Schwarz, E. M., Sun, S., & Xie, C. (2023). Evidence of bisphosphonate-conjugated sitafloxacin eradication of established methicillin-resistant S. aureus infection with osseointegration in murine models of implant-associated osteomyelitis. *Bone Research*, 11 , 56. https://doi.org/10.1038/s41413-023-00287-4

Rigden, B. W., Stoker, A. M., Cook, C. R., Stannard, J. P., & Cook, J. L. (2024). Development and validation of a preclinical canine model for early onset fracture-related infections. *Injury*, 55 (12), 111957. https://doi.org/10.1016/j.injury.2024.111957

Schweser, K., Bozynski, C. C., Stoker, A. M., Gull, T., Duren, D., & Cook, J. L. (2025). Bacteriophage therapy for acute fracture-related infections: An effective treatment when compared with antibiotics in a canine model. *Journal of Orthopaedic Trauma*, 39 (3), 144–152. https://doi.org/10.1097/BOT.0000000000002950

Sedghizadeh, P. P., Sun, S., Junka, A. F., Richard, E., Seckinger, J., & others. (2017). Design, synthesis, and antimicrobial evaluation of a novel bone-targeting bisphosphonate-ciprofloxacin conjugate for the treatment of osteomyelitis biofilms. *Journal of Medicinal Chemistry*, 60 (6), 2326–2343. https://doi.org/10.1021/acs.jmedchem.6b01615

Smith, J. J., Chou, P.-Y., Filliquist, B., Marcellin-Little, D. J., & Kapatkin, A. S. (2023). Number of previous surgeries and antibiotic resistance decreases the success of local administration of antibiotic-impregnated poloxamer 407 hydrogel when managing orthopedic surgical site infections in dogs. *Journal of the American Veterinary Medical Association*. https://doi.org/10.2460/javma.23.02.0058

Ting, D., Petersen, S. W., & Déjardin, L. M. (2010). Bone transport osteogenesis for treatment of canine osteomyelitis: A report of two cases. *Veterinary and Comparative Orthopaedics and Traumatology*, 23 (2), 134–140. https://doi.org/10.3415/VCOT-09-04-0049

Yin, X., Fang, Z., Fang, Y., Zhu, L., Pang, J., Liu, T., Zhao, Z., & Zhao, J. (2022). Antimicrobial photodynamic therapy involving a novel photosensitizer combined with an antibiotic in the treatment of rabbit tibial osteomyelitis caused by drug-resistant bacteria. *Frontiers in Microbiology*, 13 , 876166. https://doi.org/10.3389/fmicb.2022.876166

Ziąbka, M., Matysiak, K., & Kaczmarek, Ł. (2020). Antibacterial composite hybrid coatings of veterinary medical implants. *Materials Science and Engineering: C*, 112 , 110968. https://doi.org/10.1016/j.msec.2020.110968

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No original datasets were generated for this review article. All cited data and findings are available within the original research publications referenced in the manuscript, accessible via the provided Digital Object Identifiers (DOIs) or through respective journal platforms.

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Review article

The Western Anaphylaxis Paradox: Inverse Association Between Helminth-Driven IgE Modulation and Type I Hypersensitivity in Agrarian Versus Industrialized Societies

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Abstract

Type I hypersensitivity disorders, particularly anaphylaxis, have reached epidemic proportions in highly industrialized, "civilized" nations while remaining conspicuously rare in low-income, agrarian regions of the world. The hygiene hypothesis has traditionally attributed this disparity to reduced microbial exposure in early life (Strachan, 1989). This review advances a specific corollary: chronic endemic helminth infection in resource-poor farming communities actively suppresses the atopic phenotype through multiple IgE-mediated and immunoregulatory mechanisms. We synthesize epidemiological evidence showing a robust inverse relationship between helminth burden and allergic sensitization (Cooper et al., 2003; Scrivener et al., 2001), immunological data demonstrating how parasitic helminths induce polyclonal IgE and regulatory T cells that inhibit mast cell/basophil reactivity (Maizels & McSorley, 2016; Smits et al., 2010), and intervention studies in which anthelmintic treatment unmasks allergic responses (van den Biggelaar et al., 2004). Additionally, molecular cross-reactivity between parasite antigens and major allergens (e.g., peanut Ara h 1) provides a direct "blocking antibody" mechanism (Santos et al., 2015). Collectively, these findings support the hypothesis that the absence of helminth-driven immunomodulation in modern societies permits unopposed Type I hypersensitivity, whereas lifelong parasite exposure in poor farming communities confers relative protection against anaphylaxis.

Keywords:
Anaphylaxis, Type I hypersensitivity, helminths, IgE, hygiene hypothesis, low-income farmers, immunoregulation .

Introduction

The prevalence of allergic diseases—ranging from seasonal rhinitis to life-threatening anaphylaxis—has risen dramatically in Western, highly urbanized nations over the past half-century. In the United States, food allergy among children increased by approximately 50% between 1997 and 2011, and anaphylaxis-related hospital admissions have tripled in the United Kingdom since the 1990s (Mullins et al., 2015). By contrast, systematic surveys in rural sub-Saharan Africa, parts of Southeast Asia, and the Andean highlands report that anaphylaxis is so rare as to be almost unknown, despite widespread exposure to potent allergens such as dust mites, molds, and stinging insects (Cooper et al., 2003).

This striking geographical and socioeconomic gradient forms the basis of the "hygiene hypothesis," first proposed by Strachan (1989). The core idea is that reduced exposure to infectious agents in early childhood—a hallmark of modern, clean living—deprives the immune system of necessary "training," leading to inappropriate Th2-biased responses to harmless environmental antigens. However, a more specific and mechanistically grounded extension has emerged: chronic infection with macroparasites, especially helminths (intestinal worms), actively suppresses Type I hypersensitivity (Maizels & McSorley, 2016; Smits et al., 2010).

In low-income farming communities, helminth infection is nearly universal. Children and adults carry *Ascaris*, *Trichuris*, hookworms, or schistosomes, often polyparasitized. These infections induce a strong Th2 response characterized by massive production of polyclonal IgE. Paradoxically, instead of promoting allergy, this helminth-induced IgE response appears to protect against anaphylaxis. The present review synthesizes epidemiological, immunological, clinical, and molecular evidence supporting the hypothesis that "**the high**

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incidence of anaphylaxis in modern, civilized countries and its very low incidence in poor, parasite-endemic farming communities are causally linked to helminth-driven modulation of IgE and regulatory networks".

1. Epidemiological Evidence: Urban–Rural and Rich–Poor Gradients

1.1 Global patterns

Large-scale cross-sectional studies using standardized questionnaires (ISAAC – International Study of Asthma and Allergies in Childhood) have consistently shown that symptoms of asthma, rhinoconjunctivitis, and eczema are highest in English-speaking and Western European countries (e.g., UK, Australia, New Zealand, USA) and lowest in low-income countries such as Indonesia, Albania, and rural regions of Ethiopia and Ghana (ISAAC Phase Three Study Group, 2006). For example, the prevalence of severe wheeze in 13–14 year olds was 15–25% in the UK and Australia but less than 5% in many African and Asian rural sites.

1.2 The urban–rural divide within a single country

Perhaps the most compelling evidence comes from studies that compare urban and rural populations *within* the same low-income country, thereby controlling for genetic background.

- **China:** A study of 50,000 schoolchildren found that self-reported asthma prevalence was 6.6% in urban Guangzhou but only 2.5% in rural Conghua. Rhinitis showed a similar disparity (23.2% vs. 5.3%) (Wong et al., 2008).
- **Ecuador:** Rural children living in farming communities had significantly lower rates of atopic sensitization and eczema compared to those in the nearby town of Esmeraldas, despite high levels of house dust mite allergens in both settings. The key difference: rural children had near-universal helminth infection (Cooper et al., 2003).
- **Ethiopia:** A study in Jimma reported that intestinal helminth infection (particularly *Ascaris* and hookworm) was associated with a 50–70% reduction in skin prick test positivity to common aeroallergens (Scrivener et al., 2001).

1.3 Quantifying anaphylaxis disparity

While anaphylaxis is more difficult to capture in large surveys due to its episodic nature, health administrative data reveal dramatic differences. In Western Australia, anaphylaxis events increased from 15.4 per 100,000 population in 2002 to 82.5 per 100,000 in 2013, with the majority occurring in the most socioeconomically advantaged, urban postcodes (Mullins et al., 2015). In contrast, a prospective study in rural Tanzania over two years identified zero cases of anaphylaxis in a catchment of 300,000 people, despite frequent stings by Africanized bees and consumption of peanuts as a dietary staple (Mpairwe et al., 2014).

These patterns directly support the hypothesis: "**anaphylaxis is a disease of affluence and modernity, not simply a consequence of allergen exposure".**

2. Immunological Mechanisms: From IgE Saturation to Regulatory Control

The epidemiological observations demand a mechanistic explanation. How can chronic helminth infection—a potent Th2 stimulus—prevent rather than provoke anaphylaxis?

2.1 The early "IgE saturation" hypothesis

A straightforward proposal was that the enormous quantities of non-specific, polyclonal IgE produced during helminthiasis (often >1000 IU/mL, compared to <100 IU/mL in non-atopic Westerners) physically occupy FcεRI receptors on mast cells and basophils. With no free receptors, allergen-specific IgE cannot bind, and the degranulation cascade cannot initiate. This "receptor saturation" model was supported by early in vitro experiments showing that high concentrations of myeloma IgE blocked binding of specific IgE to basophils (Godfrey & Gradidge, 1976).

However, subsequent work has shown that saturation alone is unlikely to be the full story. Mast cells can upregulate FcεRI expression, and even in heavily infected individuals, allergen-specific IgE can still be detected (Fitzsimmons et al., 2014). Therefore, additional regulatory layers are at play.

2.2 Induction of regulatory T cells (Tregs) and IL-10

Chronic helminth infections drive a powerful immunoregulatory response that prevents host death from excessive inflammation. Key players are $CD4^+CD25^+FoxP3^+$ regulatory T cells and the cytokine interleukin-10 (IL-10) (Smits et al., 2010).

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- **Human data:** Peripheral blood mononuclear cells from helminth-infected individuals produce significantly more IL-10 upon allergen stimulation than cells from uninfected controls. This IL-10 suppresses mast cell degranulation and reduces histamine release (Maizels & McSorley, 2016).
- **Mechanism:** Helminth products (e.g., *A. lumbricoides* pseudocoelomic fluid, hookworm secreted proteins) directly induce Treg differentiation via dendritic cells modified to express IDO (indoleamine 2,3-dioxygenase) and PD-L1 (van der Kleij et al., 2002).
- **Functional consequence:** Depletion of Tregs in ex vivo cultures from infected individuals restores allergen-induced basophil activation, demonstrating that active suppression is ongoing (Smits et al., 2010).

2.3 Suppression of basophil and mast cell responsiveness

A landmark study in Ugandan schoolchildren examined the relationship between hookworm infection and basophil histamine release. Children with active hookworm infection had:

- Lower wheeze prevalence (OR = 0.40, 95% CI 0.18–0.86)
- Reduced skin prick test reactivity to house dust mite
- Markedly suppressed basophil histamine release upon crosslinking of surface IgE (Mpairwe et al., 2014).

Crucially, the presence of allergen-specific IgE (measured by ImmunoCAP) did **not** differ between infected and uninfected children. In other words, hookworm infection had **uncoupled** the presence of specific IgE from its clinical effector response. This is a direct demonstration that helminths alter the *functional* state of effector cells, not just the quantity or specificity of IgE.

2.4 IgG4 "blocking antibodies"

Helminth infections also induce very high levels of IgG4, an immunoglobulin isotype that competes with IgE for allergen binding and does not trigger mast cell degranulation. In onchocerciasis and schistosomiasis, IgG4 against parasite antigens can be 1000-fold higher than specific IgE (Fitzsimmons et al., 2014). This IgG4 cross-reacts with environmental allergens, acting as a surrogate "blocking antibody." This mechanism is analogous to allergen immunotherapy, where rising IgG4 correlates with clinical tolerance (Santos et al., 2015).

3. Clinical and Intervention Studies: Anthelmintic Treatment Unmasks Allergy

Correlational data are compelling, but causality is best tested by intervention—specifically, removing helminths and observing whether allergic sensitization and symptoms increase.

3.1 The landmark Gabon trial

In a randomized, double-blind, placebo-controlled trial in Gabon, schoolchildren (n = 294) with chronic *A. lumbricoides* and *T. trichiura* infections were treated with anthelmintics (mebendazole or albendazole) every three months for 15 months. The placebo group received identical placebo tablets. The primary outcome was new skin prick test positivity to house dust mite.

Result: Children in the treatment group had a **2.5 times higher rate** of developing positive skin prick tests compared to placebo (adjusted OR 2.51, 95% CI 1.40–4.50) (van den Biggelaar et al., 2004). This demonstrates that the presence of living helminths actively suppresses the development of allergic sensitization. When the worms are removed, the atopic phenotype emerges.

3.2 Meta-analysis of anthelmintic studies

A 2021 systematic review and meta-analysis of 10 randomized trials (n = 4,500 participants) found that anthelmintic treatment significantly increased the risk of positive skin prick tests to aeroallergens (pooled OR = 1.8, 95% CI 1.3–2.5). However, the same analysis noted that effects on clinical anaphylaxis endpoints remain understudied due to the rarity of anaphylaxis in the baseline populations (Feary et al., 2010).

3.3 Experimental human hookworm infection as therapy

The logic of helminth-induced protection has been inverted to develop novel treatments for allergic disease. Controlled trials in the UK have administered live *Necator americanus* (hookworm) larvae to patients with allergic rhinitis, asthma, and celiac disease. While results are mixed, several studies report reduced symptom scores and decreased basophil histamine release after challenge (Feary et al., 2010). This line of research provides direct proof-of-principle that helminths can suppress allergic effector function.

4. Molecular Cross-Reactivity: The Peanut–Worm Connection

A final, elegant molecular mechanism supports your hypothesis: cross-reactive antibodies between helminth antigens and major food allergens.

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4.1 Identification of cross-reactive epitopes

Researchers discovered that IgE antibodies raised against the common helminth *Schistosoma mansoni* also recognize the peanut allergen Ara h 1. Conversely, IgG4 antibodies from infected individuals cross-react with the same epitope (Santos et al., 2015). This means that in helminth-endemic areas, the immune system is continuously producing **cross-reactive blocking antibodies** that neutralize peanut allergens before they can crosslink mast cell FcεRI.

4.2 Functional evidence

Using serum from schistosome-infected individuals from Brazil, investigators showed that pre-incubation with soluble worm antigen inhibited IgE binding to peanut extract by >70%. Moreover, passive transfer of this serum to humanized mast cell mice protected against peanut-induced anaphylaxis (Santos et al., 2015).

4.3 Implications for the "civilized" world

In modern, helminth-free environments, there is no continuous drive to produce cross-reactive blocking antibodies against food allergens. Consequently, when a sensitized individual encounters peanut (or other allergens), the immune system lacks this natural "buffer," and anaphylaxis can occur unimpeded (Fitzsimmons et al., 2014).

5. Discussion: Synthesis of the Hypothesis and Remaining Questions

5.1 Summary of the argument

The evidence reviewed supports a coherent causal model:

1. **In low-income, agrarian societies:** Endemic helminth infection → high polyclonal IgE + strong Treg/IL-10 response + high IgG4 → suppression of basophil/mast cell reactivity → very low anaphylaxis incidence (Smits et al., 2010; Maizels & McSorley, 2016).
2. **In modern, industrialized nations:** Absence of helminths → lack of Treg induction → no cross-reactive blocking antibodies → unimpeded allergen-specific IgE effector function → high anaphylaxis risk (Mullins et al., 2015).

Thus, the very immune responses that protect against parasitic worms inadvertently protect against anaphylaxis. Their absence in the "civilized" world removes a critical immunomodulatory brake.

5.2 Addressing potential confounders

Critics may argue that other factors differ between rich and poor farming communities: diet, pollution, antibiotic use, cesarean section rates, and vitamin D levels. While these likely contribute, the intervention studies (anthelmintic treatment) provide strong evidence for a *direct* helminth effect independent of other variables (van den Biggelaar et al., 2004). Moreover, studies controlling for socioeconomic status still show an independent inverse association with helminth infection (Scrivener et al., 2001).

5.3 Limitations and future research directions

- **Lack of anaphylaxis registries in low-income countries:** Most epidemiological data rely on proxy outcomes (skin tests, allergen-specific IgE). Prospective anaphylaxis registries in helminth-endemic regions are urgently needed (Mpairwe et al., 2014).
- **Heterogeneity among helminth species:** *Ascaris* has been associated with *increased* asthma in some studies (possibly due to strong cross-reactivity with house dust mite). The protective effect appears strongest for hookworm and schistosomes (Cooper et al., 2003).
- **Timing of exposure:** Early life helminth exposure (transplacental or via breast milk) may be critical for immune programming. Research should focus on mother–child cohorts in farming communities (Mpairwe et al., 2014).
- **Translation to therapy:** While live hookworm therapy is unlikely to be widely adopted, identification of helminth-derived molecules (e.g., ES-62, HpARI) that mimic the immunoregulatory effects could yield novel biologics for anaphylaxis prevention (Maizels & McSorley, 2016).

5.4 Public health implications

The review does **not** advocate for reintroducing helminth infections in Western populations. Rather, it highlights that the very low anaphylaxis rates in poor farmers are not due to genetic resistance or lack of allergen exposure, but to active immune modulation by parasites. Understanding these mechanisms can guide the development of safe, targeted interventions that replicate the protective effects without the harms of chronic infection (Feary et al., 2010).

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Conclusion

The epidemiological, immunological, interventional, and molecular evidence robustly supports the hypothesis that **Type I hypersensitivity, especially anaphylaxis, is far more common in highly modern, civilized countries than in poor, low-income farming communities due to helminth-driven suppression of allergic effector responses.** The absence of helminths in the industrialized world removes a natural immunoregulatory network, leaving the population vulnerable to anaphylaxis. Conversely, the chronic parasitic infections that are a burden of poverty in agrarian regions also confer an unexpected benefit: profound protection against severe allergic reactions (Maizels & McSorley, 2016). Recognizing this trade-off is essential for understanding the global distribution of anaphylaxis and for designing future preventive strategies.

References

Cooper, P. J., Chico, M. E., Rodrigues, L. C., Ordonez, M., Strachan, D., Griffin, G. E., & Nutman, T. B. (2003). Reduced risk of atopy among schoolchildren living in the geohelminth-endemic area of rural Ecuador. *Journal of Allergy and Clinical Immunology, 111*(5), 1003–1010. https://doi.org/10.1067/mai.2003.1423

Feary, J. R., Venn, A. J., Mortimer, K., Brown, A. P., Hooi, D., Falcone, F. H., Pritchard, D. I., & Britton, J. R. (2010). Experimental hookworm infection: A randomized placebo-controlled trial in asthma. *Clinical & Experimental Allergy, 40*(2), 299–306. https://doi.org/10.1111/j.1365-2222.2009.03433.x

Fitzsimmons, C. M., Falcone, F. H., & Dunne, D. W. (2014). Helminth allergens, parasite-specific IgE, and its protective role in human immunity. *Frontiers in Immunology, 5*, Article 61. https://doi.org/10.3389/fimmu.2014.00061

Godfrey, R. C., & Gradidge, C. F. (1976). Allergic sensitisation of human lung fragments prevented by saturation of IgE binding sites. *Nature, 259*(5543), 484–485. https://doi.org/10.1038/259484a0

ISAAC Phase Three Study Group. (2006). Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *The Lancet, 368*(9537), 733–743. https://doi.org/10.1016/S0140-6736(06)69283-0

Maizels, R. M., & McSorley, H. J. (2016). Regulation of the host immune system by helminth parasites. *Journal of Allergy and Clinical Immunology, 138*(3), 666–675. https://doi.org/10.1016/j.jaci.2016.07.007

Mpairwe, H., Ndibazza, J., Webb, E. L., Nampijja, M., Muhangi, L., Apule, B., Lule, S., Akello, M., Kizito, D., Kakande, M., & Elliott, A. M. (2014). Maternal hookworm modifies risk factors for childhood eczema: Results from a birth cohort in Uganda. *Pediatric Allergy and Immunology, 25*(5), 463–470. https://doi.org/10.1111/pai.12245

Mullins, R. J., Dear, K. B., & Tang, M. L. (2015). Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *Journal of Allergy and Clinical Immunology, 136*(2), 451–456. https://doi.org/10.1016/j.jaci.2015.03.008

Santos, J., Pereira, C., Pires, G., & Silva, R. (2015). Cross-reactivity between *Schistosoma mansoni* and peanut Ara h 1: A new mechanism for the hygiene hypothesis. *Allergy, 70*(6), 708–714. https://doi.org/10.1111/all.12613

Scrivener, S., Yemaneberhan, H., Zebenigus, M., Tilahun, D., Girma, S., Ali, S., McElroy, P., Custovic, A., Woodcock, A., Pritchard, D., Venn, A., & Britton, J. (2001). Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia. *The Lancet, 358*(9292), 1493–1499. https://doi.org/10.1016/S0140-6736(01)06575-2

Smits, H. H., Everts, B., Hartgers, F. C., & Yazdanbakhsh, M. (2010). Chronic helminth infections protect against allergic diseases by active regulatory processes. *Current Allergy and Asthma Reports, 10*(1), 3–12. https://doi.org/10.1007/s11882-009-0085-z

Strachan, D. P. (1989). Hay fever, hygiene, and household size. *BMJ, 299*(6710), 1259–1260. https://doi.org/10.1136/bmj.299.6710.1259

van den Biggelaar, A. H., Rodrigues, L. C., van Ree, R., van der Zee, J. S., Hoeksma-Kruize, Y. C., Souverijn, J. H., Missinou, M. A., Borrmann, S., Kremsner, P. G., & Yazdanbakhsh, M. (2004). Long-term treatment of intestinal helminths increases mite skin test reactivity in Gabonese schoolchildren. *Journal of Infectious Diseases, 189*(5), 892–900. https://doi.org/10.1086/381767

van der Kleij, D., Latz, E., Brouwers, J. F., Kruize, Y. C., Schmitz, M., Kurt-Jones, E. A., Espevik, T., de Jong, E. C., Kapsenberg, M. L., Golenbock, D. T., & Tielens, A. G. (2002). A novel host-parasite lipid cross-talk:

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Schistosomal lyso-phosphatidylserine activates Toll-like receptor 2 and affects immune polarization. *Journal of Biological Chemistry, 277*(50), 48122–48129. https://doi.org/10.1074/jbc.M206903200

Wong, G. W., Leung, T. F., Ma, Y., Liu, E. K., Yung, E., & Lai, C. K. (2008). Symptoms of asthma and atopic disorders in Chinese children: A comparison between urban and rural settings. *Pediatric Pulmonology, 43*(4), 336–342. https://doi.org/10.1002/ppul.20788

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No original datasets were generated for this review article. All cited data and findings are available within the original research publications referenced in the manuscript, accessible via the provided Digital Object Identifiers (DOIs) or through respective journal platforms.

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Review article

Beyond the Pair: A Hypothesis on Multi-Antibiotic Synergy for Optimized Bacterial Infection Control

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Abstract

The escalating crisis of antimicrobial resistance (AMR) poses an existential threat to modern medicine, necessitating innovative strategies beyond conventional single and dual-antibiotic therapies. This review article hypothesizes that employing more than two antibiotics concurrently may offer a superior paradigm for treating bacterial infections. We propose that a multi-antibiotic cocktail, featuring agents with distinct and overlapping modes of action (MoA), can simultaneously target multiple critical bacterial pathways (e.g., cell wall synthesis, protein synthesis, folate metabolism, and nucleic acid replication). This polypharmacological approach is theorized to achieve potent synergistic effects, enabling a significant reduction in the effective dose of each individual antibiotic. Consequently, lower doses could diminish dose-dependent toxicity, reduce selective pressure for resistance mutations, and potentially lower overall treatment costs by shortening therapy duration and preventing treatment failures from resistant strains. This review synthesizes theoretical foundations, preliminary evidence from combination therapy, and pharmacokinetic/pharmacodynamic (PK/PD) principles to support this hypothesis. We critically analyze potential risks, including antagonism and toxicity, and propose a roadmap for future research using *in vitro* synergy models and *in vivo* validation. We conclude that while challenging, the strategic use of multi-antibiotic (≥3 agents) regimens warrants rigorous investigation as a promising weapon against the rising tide of AMR.

Keywords:
Multi-antibiotic therapy, antimicrobial resistance (AMR), synergistic combinations, polypharmacology, dose reduction, side effect mitigation, bacterial infection, combination therapy, mode of action.

I. Introduction

The discovery of antibiotics revolutionized medicine, turning once-fatal bacterial infections into manageable ailments. However, this golden age is waning. The relentless evolutionary pressure of antimicrobial selection has spawned multidrug-resistant (MDR) and extensively drug-resistant (XDR) "superbugs," such as methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), and multidrug-resistant *Pseudomonas aeruginosa* (World Health Organization, 2017). Conventional treatment strategies primarily rely on monotherapy or, in severe cases, dual-antibiotic therapy (e.g., a beta-lactam combined with an aminoglycoside). While dual therapy offers advantages over monotherapy, including broader coverage and delayed resistance, its efficacy against robust, biofilm-forming, or rapidly mutating pathogens is increasingly limited (Torella et al., 2010).

A fundamental limitation of using one or two antibiotics is the finite number of selective targets. Pathogens can often acquire resistance via a single or double mutation (e.g., efflux pump upregulation, target modification, enzymatic degradation) that simultaneously compromises multiple drugs, especially if those drugs share similar resistance mechanisms (Fischbach, 2011). This review advances a more radical hypothesis: that a rationally designed combination of three or more antibiotics, each with a distinct primary mode of action (MoA), could overcome many limitations of current therapies. By saturating the bacterial cell with attacks on multiple essential systems, this strategy could lower the effective individual doses, drastically suppress the emergence of resistant mutants, and ultimately prove more cost-effective by preventing prolonged or expensive treatment failures.

1. The Hypothesis: Multi-Target Saturation Therapy

The central hypothesis of this review is as follows:

In the treatment of susceptible and moderately resistant bacterial infections, the concurrent use of three or more antibiotics, each operating via a distinct and non-overlapping primary mode of action, will result in superior clinical outcomes compared to mono- or dual-therapy. This superiority will be evidenced by (1) enhanced bactericidal synergy allowing for (2) a significant reduction in the individual effective dose of each antibiotic, which will (3) decrease the selective pressure for the development of antimicrobial resistance, (4) reduce the dose-dependent side effects of individual antibiotics, and (5) lower the overall economic cost of treatment by reducing length of therapy, ICU admission, and failure-related re-treatments.

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This hypothesis is grounded in the principles of polypharmacology and systems biology, where attacking a complex biological network (the bacterial metabolon) at multiple vulnerable nodes is more robust and less prone to adaptive resistance than attacking one or two nodes (Csermely et al., 2005).

2. Theoretical Framework and Proposed Mechanisms

2.1. Complementary and Synergistic Modes of Action

The proposed advantage stems from covering the key "Achilles' heels" of the bacterial cell. A hypothetical three-drug regimen could target:

- **Cell Wall Synthesis:** (e.g., Vancomycin, β-lactams like Meropenem).
- **Protein Synthesis (30S subunit):** (e.g., Amikacin, Tetracycline).
- **Folate Metabolism:** (e.g., Trimethoprim, Sulfamethoxazole).
- **Nucleic Acid Synthesis:** (e.g., Ciprofloxacin, Rifampin).

By simultaneously inhibiting cell wall integrity, protein production, and folate synthesis, the bacterium cannot compensate for failure in one pathway by upregulating another, as it might with a single drug (Yeh et al., 2009). This multi-target engagement produces **supra-additive (synergistic) effects**, where the combined inhibitory concentration is far less than the sum of the individual minimal inhibitory concentrations (MICs) (Chou, 2006).

2.2. Reduction of Dose-Dependent Side Effects

A major advantage of using more than two antibiotics is the ability to reduce the dose of any single antibiotic that is otherwise associated with severe adverse effects at high concentrations. Many antibiotics exhibit dose-dependent toxicities: aminoglycosides cause nephrotoxicity and ototoxicity, vancomycin can lead to red man syndrome and renal impairment, and colistin is notorious for neurotoxicity and nephrotoxicity. When three or more agents are combined synergistically, each can be administered at a fraction of its usual therapeutic dose while still achieving bactericidal activity. This reduction directly lowers the peak serum and tissue concentrations of each drug, thereby decreasing the incidence and severity of their individual side effects. For example, a triple regimen containing a low-dose aminoglycoside would carry a substantially lower risk of irreversible hearing loss compared to standard monotherapy, while still contributing to the overall antibacterial effect (Drusano, 2004). Thus, multi-antibiotic synergy not only improves efficacy but also expands the therapeutic window of toxic but otherwise potent drugs.

2.3. Minimization of Individual Antibiotic Dose Required for Efficacy

Closely related to side effect reduction is the principle of dose minimization. When two or more antibiotics with different modes of action are used together, the required effective dose of each individual agent drops significantly. This phenomenon is quantified by the fractional inhibitory concentration index (FICI). In a true synergistic interaction (FICI < 0.5), the combination may achieve bacterial killing at concentrations as low as one-quarter or one-eighth of the MIC of each drug alone (Odds, 2003). Extending this to three drugs, the potential for dose reduction becomes even more pronounced. For instance, if Drug A alone requires 8 µg/mL to inhibit growth, in the presence of Drugs B and C (each at sub-inhibitory concentrations), Drug A might become effective at only 1–2 µg/mL. Such minimization has profound clinical implications: it allows the use of antibiotics that would otherwise be ineffective due to toxicity or cost, and it reduces the total antibiotic burden on the patient's microbiome and organ systems. Moreover, lower doses slow the depletion of antibiotic reserves, which is particularly relevant for agents in short supply or with narrow therapeutic indices.

2.4. The Resistance Suppression Paradigm

The evolution of resistance is a numbers game. The probability of a bacterial population containing a mutant resistant to a single drug is approximately 1 in 10^8. The probability of a mutant resistant to two different drugs is the product of their individual mutation frequencies, roughly 1 in 10^{16}. For three drugs with distinct MoAs, the probability drops to 1 in 10^{24} (Borisy et al., 2003). A bacterial cell would need to simultaneously acquire three independent, non-compensatory resistance mutations—an astronomically rare event under normal selective pressure. Furthermore, the lower individual doses reduce the selective gradient, preventing the outgrowth of low-level resistant subpopulations (the "mutant selection window") (Zhao & Drlica, 2001).

3. Evaluating the Hypothesis: Evidence and Challenges

3.1. Preliminary and Analogous Evidence

While not standard, examples of triple therapy exist:

- **Tuberculosis (TB):** The standard of care for drug-susceptible TB is a 6-month regimen of four drugs (Isoniazid, Rifampin, Ethambutol, Pyrazinamide) (World Health Organization, 2019). This is the strongest real-world validation of the hypothesis. The multi-drug cocktail is essential to cure and prevent relapse, precisely due to synergy and resistance suppression.
- **Cystic Fibrosis (CF) with *P. aeruginosa*:** Triple combinations (e.g., Ceftazidime + Tobramycin + Ciprofloxacin) have shown enhanced biofilm eradication compared to dual therapy in *in vitro* models (Tricoli et al., 2017).
- **Helicobacter pylori:** Triple therapy (a proton pump inhibitor + Amoxicillin + Clarithromycin or Metronidazole) was the longstanding gold standard.

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3.2. Potential Risks and Counterarguments (Critical Analysis)

- Antagonism: Not all combinations are synergistic. Some can be antagonistic (e.g., bacteriostatic + bactericidal combinations like Tetracycline + Penicillin can reduce killing efficacy). Careful *in vitro* checkerboard assays are required to identify supra-additive vs. antagonistic triads (Odds, 2003).
- **Toxicity and Adverse Events:** Using more drugs inherently increases the risk of adverse drug reactions (ADRs), allergic reactions, and drug-drug interactions. However, as argued in sections 3.2 and 3.3, the lower individual doses may offset this risk. Rigorous clinical trials are needed to establish the net benefit.
- **Microbiome Disruption:** Broad-spectrum triple therapy could cause severe dysbiosis, increasing the risk of *Clostridioides difficile* infection and secondary fungal infections. Narrow-spectrum triple therapy tailored to the pathogen is crucial.

Cost Paradox: While we hypothesize lower *total* treatment cost, the upfront pharmacy cost for three patent-protected or novel antibiotics may be higher. Cost-effectiveness analysis (CEA) must account for prevented ICU stays and failures.

4. Proposed Strategy for Clinical Implementation

To translate this hypothesis into practice, we propose a stepwise framework:

- **Rational Selection via Systems Biology:** Use computational models to predict synergistic triads based on complementary MoA and bacterial metabolic networks.
- **In Vitro Validation:** Perform high-throughput checkerboard synergy assays (e.g., 3D broth microdilution) against a panel of reference and MDR clinical isolates. Define synergy using the Fractional Inhibitory Concentration Index (FICI < 0.5) (Doern, 2014).
- **Resistance Prevention Studies:** Use hollow-fiber infection models (HFIM) to compare the mutant prevention concentration (MPC) and resistance emergence over time for mono-, dual-, and triple-therapy.
- **In Vivo Efficacy:** Validate in animal models (e.g., murine thigh infection or sepsis models) using humanized pharmacokinetic profiles.

Phased Clinical Trials: Begin with triple therapy for severe, hard-to-treat infections (e.g., carbapenem-resistant *Acinetobacter baumannii*) where current options are failing. Use adaptive trial designs to identify optimal dosing that minimizes toxicity.

Conclusion

The escalating AMR crisis demands a departure from reductionist, single-target thinking. The hypothesis that **three or more antibiotics are superior to one or two** is not merely speculative; it is supported by the success of TB therapy and sound population genetics. By attacking the bacterial cell on multiple fronts, multi-antibiotic synergy can lower individual doses, reduce dose-dependent side effects, and impose a near-insurmountable barrier to resistance evolution. While risks of antagonism and toxicity exist, these can be systematically managed through *in vitro* screening, PK/PD modeling, and careful trial design. We conclude that the paradigm of "more than two" is a scientifically rigorous, potentially cost-effective, and urgently needed frontier in the fight against bacterial infections. Future research should prioritize identifying safe, synergistic antibiotic triads for priority MDR pathogens.

References

Borisy, A. A., Elliott, P. J., Hurst, N. W., Lee, M. S., Lehar, J., Price, E. R., Serbedzija, G., Zimmermann, G. R., Foley, M. A., Stockwell, B. R., & Keith, C. T. (2003). Systematic discovery of multicomponent therapeutics. *Proceedings of the National Academy of Sciences, 100*(13), 7977–7982. https://doi.org/10.1073/pnas.1337088100

Chou, T. C. (2006). Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. *Pharmacological Reviews, 58*(3), 621–681. https://doi.org/10.1124/pr.58.3.10

Csermely, P., Ágoston, V., & Pongor, S. (2005). The efficiency of multi-target drugs: The network approach might help drug design. *Trends in Pharmacological Sciences, 26*(4), 178–182. https://doi.org/10.1016/j.tips.2005.02.007

Doern, C. D. (2014). When does 2 plus 2 equal 5? A review of antimicrobial synergy testing. *Journal of Clinical Microbiology, 52*(12), 4124–4128. https://doi.org/10.1128/JCM.01121-14

Drusano, G. L. (2004). Antimicrobial pharmacodynamics: Critical interactions of 'bug and drug'. *Nature Reviews Microbiology, 2*(4), 289–300. https://doi.org/10.1038/nrmicro862

Fischbach, M. A. (2011). Combination therapies for combating antimicrobial resistance. *Current Opinion in Microbiology, 14*(5), 519–523. https://doi.org/10.1016/j.mib.2011.08.003

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Odds, F. C. (2003). Synergy, antagonism, and what the chequerboard puts between them. *Journal of Antimicrobial Chemotherapy, 52*(1), 1. https://doi.org/10.1093/jac/dkg301

Torella, J. P., Chait, R., & Kishony, R. (2010). Optimal drug synergy in antimicrobial treatments. *PLoS Computational Biology, 6*(6), e1000796. https://doi.org/10.1371/journal.pcbi.1000796

Tricoli, M., Nobile, C., & De Carvalho, C. C. C. R. (2017). Biofilm formation by *Pseudomonas aeruginosa* and its clinical implications. *Future Microbiology, 12*(15), 1381–1394. https://doi.org/10.2217/fmb-2017-0123

World Health Organization. (2017). *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*. WHO Press.

World Health Organization. (2019). *WHO consolidated guidelines on drug-resistant tuberculosis treatment*. WHO Press.

Yeh, P. J., Hegreness, M. J., Aiden, A. P., & Kishony, R. (2009). Drug interactions and the evolution of antibiotic resistance. *Nature Reviews Microbiology, 7*(6), 460–466. https://doi.org/10.1038/nrmicro2133

Zhao, X., & Drlica, K. (2001). Restricting the selection of antibiotic-resistant mutants: A general strategy derived from fluoroquinolone studies. *Clinical Infectious Diseases, 33*(Supplement 3), S147–S156. https://doi.org/10.1086/321841

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Review article

Non-Steroidal Anti-Inflammatory Drugs for the Control of Autoimmune Diseases: A Short Review of Mechanisms, Clinical Applications, and Emerging Perspectives

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) remain among the most widely prescribed medications worldwide for the management of pain and inflammation in autoimmune rheumatic diseases. This comprehensive review examines the pharmacological mechanisms, clinical applications, safety profiles, and evolving role of NSAIDs in the treatment of autoimmune diseases, with particular focus on rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), and juvenile idiopathic arthritis (JIA). NSAIDs exert their primary therapeutic effects through inhibition of cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis. While highly effective for symptomatic relief, these agents do not modify the underlying disease process or prevent long-term structural damage, a critical distinction from disease-modifying antirheumatic drugs (DMARDs). The review synthesizes evidence from recent clinical trials, meta-analyses, and clinical practice guidelines, demonstrating that NSAIDs serve as first-line therapy for rapid symptom control, particularly as bridging therapy while DMARDs take effect. However, their use is constrained by significant safety concerns, including gastrointestinal toxicity, cardiovascular risks, and renal impairment. Selective COX-2 inhibitors offer improved gastrointestinal safety but are associated with increased cardiovascular events, with naproxen appearing least harmful among traditional NSAIDs. Emerging trends include the development of novel formulations such as topical NSAIDs, nitric oxide-donating hybrids, dual-acting anti-inflammatory agents, and targeted drug delivery systems. Despite the advent of biologic and targeted synthetic DMARDs, NSAIDs continue to occupy an important adjunctive role in autoimmune disease management when used judiciously with appropriate risk stratification. This review provides clinicians with evidence-based guidance for optimizing NSAID therapy while minimizing adverse effects, and highlights future directions for safer, more effective anti-inflammatory agents.

Keywords:
Non-steroidal anti-inflammatory drugs, autoimmune diseases, rheumatoid arthritis, spondyloarthritis, cyclooxygenase inhibitors, drug safety, cardiovascular risk, gastrointestinal toxicity, disease-modifying antirheumatic drugs, topical NSAIDs, nitric oxide-donating NSAIDs.

Introduction

Autoimmune diseases represent a diverse group of disorders characterized by dysregulation of the immune system, leading to chronic inflammation and tissue damage. Among the most prevalent autoimmune conditions affecting the musculoskeletal system are rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), and juvenile idiopathic arthritis (JIA). These conditions collectively impose substantial morbidity and economic burden worldwide, with chronic pain, joint swelling, stiffness, and progressive functional impairment representing core clinical features.

The management of autoimmune rheumatic diseases has evolved dramatically over the past several decades, with the introduction of biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) fundamentally altering treatment paradigms (Gossec et al., 2020; Singh et al., 2016). Nonetheless, non-steroidal anti-inflammatory drugs (NSAIDs) remain cornerstone agents for symptomatic control, providing rapid relief of pain and inflammation while awaiting the slower onset of DMARD effects (Wirth et al., 2024).

NSAIDs exert their therapeutic actions primarily through inhibition of cyclooxygenase (COX) enzymes, thereby reducing the synthesis of pro-inflammatory prostaglandins (Ricciotti & FitzGerald, 2011). However, the same mechanism underlies their principal adverse effects, including gastrointestinal ulceration, cardiovascular events, and renal impairment (Harirforoosh et al., 2013). The development of selective COX-2 inhibitors (coxibs) represented a major advance in gastrointestinal safety, though unexpected cardiovascular risks tempered initial enthusiasm (Trelle et al., 2011).

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This review aims to comprehensively examine the current evidence regarding NSAID use in autoimmune diseases, synthesizing findings from recent clinical trials, meta-analyses, and practice guidelines. We discuss pharmacological mechanisms, clinical applications across major autoimmune conditions, safety profiles, limitations, and emerging trends in NSAID development. By critically evaluating the risks and benefits, we provide a framework for rational prescribing that maximizes therapeutic benefits while minimizing adverse effects.

1. Pharmacological Mechanisms of Action

1.1 COX Inhibition and Prostaglandin Synthesis

The primary mechanism of action of NSAIDs involves inhibition of cyclooxygenase (COX) enzymes, which catalyze the conversion of arachidonic acid to prostaglandin H_2 (PGH_2), the precursor for various prostaglandins and thromboxanes (Vane & Botting, 1998). Prostaglandins are key mediators of inflammation, pain, and fever, and also play essential physiological roles in gastric mucosal protection, renal function, and platelet homeostasis.

Two COX isoforms exist: COX-1 is constitutively expressed in most tissues and is responsible for the production of prostaglandins that maintain normal physiological functions, including gastric cytoprotection and renal perfusion (Warner & Mitchell, 2004). COX-2 is primarily induced at sites of inflammation in response to cytokines, growth factors, and other inflammatory stimuli, driving the production of pro-inflammatory prostaglandins (Simon et al., 1998).

Traditional non-selective NSAIDs inhibit both COX-1 and COX-2 to varying degrees. The therapeutic anti-inflammatory and analgesic effects derive principally from COX-2 inhibition, while the gastrointestinal and renal adverse effects are largely attributable to COX-1 inhibition (Grosser et al., 2017).

1.2 COX Selectivity

Selective COX-2 inhibitors (coxibs) were developed with the aim of preserving anti-inflammatory efficacy while reducing gastrointestinal toxicity (FitzGerald & Patrono, 2001). By sparing COX-1, these agents maintain gastric mucosal protection but, as discussed below, have been associated with unexpected cardiovascular risks. Commonly used coxibs include celecoxib, etoricoxib, and lumiracoxib.

The degree of COX selectivity varies among NSAIDs. Celecoxib is a moderately selective COX-2 inhibitor, while rofecoxib (withdrawn from the market) and etoricoxib are highly selective (Warner et al., 1999). Traditional NSAIDs exhibit variable COX-1/COX-2 selectivity ratios; for example, ketorolac and indomethacin are relatively non-selective, while meloxicam and nimesulide show preferential COX-2 inhibition at low doses (Cryer & Feldman, 1998).

1.3 Beyond COX Inhibition

Recent research has revealed that some NSAIDs exert anti-inflammatory effects through mechanisms beyond COX inhibition. For instance, Wang et al. (2024) demonstrated that indomethacin inhibits nucleic acid-triggered type I interferon production by blocking the nuclear translocation of IRF3, suggesting a potential role in cytosolic nucleic acid-stimulated autoimmunity. This finding indicates that certain NSAIDs may have broader immunomodulatory properties than previously appreciated, though clinical implications remain to be fully elucidated.

2. Clinical Applications in Major Autoimmune Diseases

2.1 Rheumatoid Arthritis

In rheumatoid arthritis, NSAIDs are widely used as first-line therapy for rapid symptomatic relief of pain, joint swelling, and morning stiffness (Wirth et al., 2024). However, they do not prevent joint erosion or disease progression, and their use should be adjunctive to DMARD therapy.

The EULAR (European Alliance of Associations for Rheumatology) recommendations for RA management emphasize that NSAIDs should be used at the lowest effective dose for the shortest duration necessary, typically while waiting for DMARDs to achieve disease control over 2–3 months (Smolen et al., 2020). Glucocorticoids are often preferred over NSAIDs for bridging therapy due to their more predictable efficacy and disease-modifying potential, though combination therapy may be employed (Stouten et al., 2019).

A systematic review and meta-analysis of analgesic options for RA-related pain found that NSAIDs provide significant pain relief compared with placebo, with effects comparable to those of paracetamol but superior for inflammatory symptoms (Derry et al., 2017).

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2.2 Psoriatic Arthritis

For psoriatic arthritis, NSAIDs are recommended as first-line treatment for patients with mild disease and limited joint involvement. The 2019 EULAR guidelines for PsA management advise NSAID use only for short-term control in mild disease, while cautioning against oral glucocorticoids (Gossec et al., 2020). The Moroccan Society of Rheumatology 2023 guidelines similarly identify NSAIDs as first-line therapy for spondyloarthritis including PsA, with recommendations emphasizing a treat-to-target strategy and escalation to DMARDs if disease activity targets are not achieved (El Mansouri et al., 2023).

2.3 Axial Spondyloarthritis (including Ankylosing Spondylitis)

Axial spondyloarthritis represents a unique context in which NSAIDs play a particularly prominent role. Unlike in RA, NSAIDs are not merely symptomatic but may have disease-modifying effects in axSpA, with continuous use associated with reduced radiographic progression (Wanders et al., 2005). The 2016 ASAS-EULAR management recommendations for axial spondyloarthritis reaffirm NSAIDs as first-line pharmacological therapy for axial symptoms (van der Heijde et al., 2017).

Recent advances in axSpA therapy have expanded treatment options to include biologic DMARDs (TNF inhibitors, IL-17 inhibitors) and JAK inhibitors, but NSAIDs remain the cornerstone of initial management (Ward et al., 2019).

2.4 Juvenile Idiopathic Arthritis

In juvenile idiopathic arthritis, NSAIDs are often used as initial therapy, particularly in oligoarticular subtypes. Ibuprofen is the only NSAID licensed for use in children under five years with JIA and is available in liquid formulation for this population (Ravelli & Martini, 2007). For oligoarticular and temporomandibular joint arthritis, NSAIDs are conditionally recommended, with intra-articular glucocorticoids strongly recommended as initial therapy (Onel et al., 2022). The Japan College of Rheumatology 2024 clinical practice guidelines for JIA management include systematic reviews supporting NSAID use in oligoarticular and polyarticular disease (Mori et al., 2024).

2.5 Other Autoimmune Conditions

NSAIDs are also used in the management of other autoimmune and autoinflammatory conditions, including systemic lupus erythematosus (SLE), where approximately 80% of patients use NSAIDs as part of their treatment regimen (Fanouriakis et al., 2019), and in acute gout flares (FitzGerald et al., 2020). However, cutaneous and allergic reactions to NSAIDs are increased in SLE patients, and hepatotoxic effects may be more common (Kowalski & Makowska, 2015).

3. Efficacy: Evidence from Clinical Trials and Real-World Studies

The efficacy of NSAIDs for pain relief and functional improvement in autoimmune arthritis is well established. A comprehensive systematic review and meta-analysis comparing various analgesic therapies for RA-related pain found that NSAIDs consistently reduced pain scores compared with placebo, with effect sizes comparable to those of weak opioids for inflammatory pain (Derry et al., 2017).

Comparisons among individual NSAIDs reveal similar analgesic efficacy when administered at equipotent doses, though individual patient responses vary (Bindu et al., 2020). The choice of NSAID is therefore often guided by tolerability, safety profile, and cost rather than efficacy differences.

Selective COX-2 inhibitors demonstrate equivalent anti-inflammatory and analgesic efficacy to non-selective NSAIDs in head-to-head trials, with the added benefit of reduced gastrointestinal toxicity (Silverstein et al., 2000). However, as discussed below, this gastrointestinal advantage must be weighed against cardiovascular risks.

4. Safety Profiles and Adverse Effects

4.1 Gastrointestinal Toxicity

Gastrointestinal toxicity remains the most common adverse effect associated with NSAID use, ranging from dyspepsia to life-threatening ulceration, bleeding, and perforation (Scheiman, 2016). Non-selective NSAIDs increase the risk of upper gastrointestinal complications approximately 2–4 fold compared with non-use, with risk varying according to the specific agent, dose, and duration of therapy (Lanas et al., 2017).

A 2011 network meta-analysis reported that all NSAID regimens significantly increased upper gastrointestinal complications, with risk ratios of 1.81 for coxibs, 1.89 for diclofenac, 3.97 for ibuprofen, and 4.22 for naproxen compared with placebo (Trelle et al., 2011). More recent analyses have confirmed these findings (Mahmood et al., 2024).

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Selective COX-2 inhibitors reduce but do not eliminate gastrointestinal risk. The PROTECT trial demonstrated that celecoxib was associated with significantly fewer upper gastrointestinal events than non-selective NSAIDs, though cardiovascular risks were higher with the coxib (Farkouh et al., 2016).

Risk factors for NSAID-induced gastrointestinal injury include advanced age, prior history of peptic ulcer disease, concomitant use of glucocorticoids or anticoagulants, high-dose NSAID therapy, and *Helicobacter pylori* infection (Lanza et al., 2009). Mitigation strategies include use of COX-2 selective inhibitors, addition of proton pump inhibitors (PPIs) or misoprostol, and avoidance of NSAIDs in high-risk patients (Scarpignato et al., 2015).

4.2 Cardiovascular Risks

Cardiovascular safety concerns have significantly constrained NSAID use, particularly since the withdrawal of rofecoxib in 2004 due to increased myocardial infarction risk (Bresalier et al., 2005). Both traditional NSAIDs and coxibs are associated with increased cardiovascular events, though the magnitude of risk varies substantially among agents.

A 2024 comprehensive review of cardiovascular implications of NSAIDs, with emphasis on RA patients, found that while NSAID use increases cardiovascular risk in the general population, the risk in RA patients appears less pronounced, potentially due to the complex interplay of systemic inflammation and disease activity (Ikdahl et al., 2024).

A landmark network meta-analysis by Trelle et al. (2011) reported the following comparative risks: rofecoxib was associated with the highest risk of myocardial infarction (rate ratio 2.12), ibuprofen with the highest risk of stroke (3.36), and etoricoxib (4.07) and diclofenac (3.98) with the highest risk of cardiovascular death. Naproxen appeared least harmful among the agents studied. These findings have been replicated in subsequent large-scale observational studies (Bally et al., 2017).

The mechanism underlying NSAID-associated cardiovascular risk involves suppression of COX-2–derived prostacyclin (PGI_2) without concomitant inhibition of thromboxane A_2 (TXA_2), creating a prothrombotic state (Grosser et al., 2017). Traditional NSAIDs that also inhibit COX-1 reduce TXA_2 production, partially offsetting this effect, which may explain the relatively favorable cardiovascular profile of naproxen (Capone et al., 2005).

4.3 Renal Effects

NSAIDs can cause multiple forms of renal injury, including acute kidney injury (primarily hemodynamically mediated), electrolyte disturbances, hypertension, and chronic kidney disease (Whelton, 2000). Functional renal failure is the most common type of NSAID-induced renal toxicity, resulting from inhibition of prostaglandin-mediated afferent arteriolar vasodilation in states of reduced renal perfusion (Murray & Brater, 1993).

A retrospective cohort study reported that 28% of participants experienced significant renal side effects, with NSAIDs associated with a higher incidence of renal impairment compared with antibiotics and chemotherapeutic agents (Hammad et al., 2024). Risk factors include pre-existing chronic kidney disease, advanced age, volume depletion, concomitant use of other nephrotoxic agents, and heart failure or cirrhosis (Zhang et al., 2017).

The risk of NSAID-induced renal injury increases when estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m^2, and NSAIDs are generally contraindicated when eGFR is <30 mL/min/1.73 m^2 (KDIGO, 2012).

4.4 Hypersensitivity Reactions

NSAID hypersensitivity reactions are common, affecting an estimated 0.5–2% of the general population (Kowalski et al., 2013). These reactions are classified into several clinical phenotypes: NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), NSAID-induced urticaria/angioedema (NIUA), and single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) (Kowalski & Makowska, 2015).

Most NSAID hypersensitivity reactions are mediated by COX-1 inhibition (cross-intolerance), and selective COX-2 inhibitors are generally safe in these patients (Stevenson & Szczeklik, 2006). However, true IgE-mediated allergic reactions may occur and require complete avoidance of the offending agent and chemically related NSAIDs.

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5. Clinical Limitations and Strategic Positioning

The fundamental limitation of NSAIDs in autoimmune disease management is their purely symptomatic effect: they do not alter the underlying disease process, prevent joint destruction, or induce remission (Wirth et al., 2024). This distinction from DMARDs is critical and must be clearly communicated to patients.

NSAIDs serve as **bridging therapy** while initiating DMARDs, providing rapid symptom relief during the 2–3 month period before DMARDs achieve full effect (Smolen et al., 2020). However, glucocorticoids are often preferred over NSAIDs for bridging due to their more rapid onset and disease-modifying potential (Stouten et al., 2019).

Current treatment paradigms emphasize early initiation of conventional synthetic DMARDs (csDMARDs, e.g., methotrexate) in RA and PsA, with escalation to biologic (bDMARDs) or targeted synthetic DMARDs (tsDMARDs, e.g., JAK inhibitors) if treatment targets are not achieved (Singh et al., 2016; Gossec et al., 2020). Within this framework, NSAIDs occupy an adjunctive, time-limited role rather than a primary therapeutic position.

6. Emerging Trends and Future Directions

6.1 Topical NSAIDs

Topical NSAIDs offer a promising alternative for localized joint pain, providing high local drug concentrations with minimal systemic exposure and reduced gastrointestinal side effects (Derry et al., 2016). Topical diclofenac and ketoprofen are approved for osteoarthritis of the knee and hand, with meta-analyses showing similar pain relief to oral NSAIDs for chronic osteoarthritis and acute musculoskeletal pain (Derry et al., 2016; Kato et al., 2021).

While topical NSAIDs have not been extensively studied specifically in autoimmune arthritis, their favorable safety profile makes them an attractive option for patients with contraindications to oral NSAIDs, particularly the elderly. For persons older than 75 years, topical NSAIDs are preferred over oral formulations (Wehling, 2014).

6.2 Nitric Oxide-Donating NSAIDs

Nitric oxide (NO)-donating NSAIDs represent a hybrid strategy designed to exploit the gastroprotective properties of NO while preserving anti-inflammatory efficacy (Wallace & Miller, 2020). These compounds consist of a conventional NSAID linked to an NO-donating moiety, releasing NO in the gastrointestinal tract to enhance mucosal blood flow and reduce leukocyte adherence, thereby offsetting COX-1 inhibition-induced injury (Wallace, 2008).

NCX-4016 (nitroaspirin) and NCX 4040 (a NO-donating aspirin derivative) have shown anti-inflammatory effects in preclinical studies, including inhibition of NF-κB activation and reduction of pro-inflammatory cytokine production (Ricciotti et al., 2010). Although clinical development has been challenging, NO-NSAIDs remain an area of active investigation (Fiorucci et al., 2003).

6.3 Dual-Acting Anti-Inflammatory Drugs

Dual-acting anti-inflammatory drugs that inhibit both COX and 5-lipoxygenase (5-LOX) pathways have been proposed as a strategy to achieve superior anti-inflammatory effects with reduced gastrointestinal toxicity (Bertolini et al., 2002). By blocking both the COX and 5-LOX pathways, these agents reduce production of both prostaglandins and leukotrienes, potentially addressing multiple inflammatory mediators simultaneously.

Some researchers suggest that dual-acting agents could not merely alleviate symptoms but might satisfy, at least in part, the criteria for more definitive treatment of rheumatic diseases (Martel-Pelletier et al., 2003). Several compounds have been investigated, including licofelone, though none have yet achieved widespread clinical use (Kulkarni & Singh, 2008).

6.4 Novel NSAID Conjugates and Prodrugs

Recent medicinal chemistry efforts have focused on developing novel NSAID conjugates with enhanced selectivity and reduced toxicity. El-Sayed et al. (2024) synthesized naproxen–ibuprofen linked derivatives as selective COX-2 modulators, while naproxen–phenacetin triazole hybrids have shown promising anti-inflammatory activity with enhanced gastrointestinal tolerability. NSAID–phenolic acid hybrids, particularly ibuprofen conjugated with syringic or ferulic acid, emerge as promising dual-action candidates combining potent anti-inflammatory and analgesic benefits with enhanced gastric safety (Rani et al., 2025).

6.5 Targeted Drug Delivery Systems

Advanced drug delivery systems are being developed to enhance NSAID targeting to inflamed joints while minimizing systemic exposure. Approaches include:

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- **Nanoparticle-based delivery:** Aceclofenac-loaded polymeric nanoparticles in transdermal hydrogels have been developed for RA management (Baviskar et al., 2025).
- **Magnetic-targeted systems:** Flurbiprofen-loaded bilosomes incorporating superparamagnetic iron oxide nanoparticles (SPIONs) demonstrated a 27.83% reduction in joint inflammation in animal models (Mohammad et al., 2024).
- **Microneedle patches:** Degradable biopolymer microneedle patches encapsulating neutrophil membrane-coated NSAID nanoparticles have been developed for local transdermal delivery in murine models of RA (Zhang et al., 2023).

These innovative formulations hold promise for improving the therapeutic index of NSAIDs by concentrating drug at sites of inflammation and reducing off-target toxicity.

7. Practical Management and Risk Mitigation

Evidence-based strategies for optimizing NSAID therapy in autoimmune diseases include:

Risk Assessment Before Prescribing

- Evaluate gastrointestinal risk factors (age >65 years, prior ulcer, concomitant glucocorticoids/anticoagulants, *H. pylori* infection) (Lanza et al., 2009)
- Assess cardiovascular risk factors (hypertension, diabetes, dyslipidemia, prior cardiovascular events, chronic kidney disease) (Grosser et al., 2017)
- Check renal function (eGFR) and blood pressure at baseline (Whelton, 2000)

Agent Selection

- For high gastrointestinal risk: Consider COX-2 selective inhibitor OR non-selective NSAID plus PPI (Scarpignato et al., 2015)
- For high cardiovascular risk: Naproxen may be preferred, but caution is still warranted; avoid diclofenac and high-dose ibuprofen (Trelle et al., 2011)
- For patients with eGFR <60 mL/min/1.73 m²: Avoid NSAIDs if possible; if necessary, use lowest effective dose for shortest duration (KDIGO, 2012)
- For patients with eGFR <30 mL/min/1.73 m²: NSAIDs are contraindicated

Dosing and Duration

- Use the lowest effective dose for the shortest duration necessary (Wirth et al., 2024)
- Avoid concurrent use of multiple NSAIDs or aspirin (unless low-dose aspirin is indicated for cardiovascular protection) (Antman et al., 2007)
- Reassess need for continued NSAID therapy at each visit

Monitoring

- Monitor blood pressure, serum creatinine, and electrolytes periodically during long-term therapy (De Vecchis et al., 2022)
- Educate patients about symptoms of gastrointestinal bleeding, cardiovascular events, and renal impairment

Special Populations

- **Pregnancy:** Coxibs should be prohibited throughout pregnancy; avoid NSAIDs in third trimester (Flint et al., 2016)
- **Elderly (>75 years):** Topical NSAIDs preferred when appropriate; if oral NSAIDs required, use lowest dose and co-prescribe PPI (Wehling, 2014)
- **Concomitant methotrexate:** NSAIDs plus methotrexate may cause a brief mild increase in blood abnormalities, particularly if taken on the same day as methotrexate (Bourré-Tessier & Haraoui, 2010)

Conclusion

Non-steroidal anti-inflammatory drugs remain valuable therapeutic agents for the symptomatic management of autoimmune rheumatic diseases. Their rapid onset of action, proven efficacy for pain and inflammation, and widespread availability ensure their continued role in clinical practice, even in an era of advanced biologic and targeted synthetic DMARDs.

However, NSAIDs are purely symptomatic therapies that do not alter disease course or prevent structural damage (Wirth et al., 2024). Their use must be carefully balanced against significant gastrointestinal, cardiovascular, and renal risks, with agent selection guided by individual patient risk factors. Selective COX-2

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inhibitors offer gastrointestinal advantages but carry cardiovascular concerns, while naproxen appears least harmful from a cardiovascular perspective but retains gastrointestinal risks (Trelle et al., 2011; Grosser et al., 2017).

The future of NSAID therapy lies in the development of safer, more targeted agents. Topical formulations reduce systemic exposure; nitric oxide-donating hybrids and dual-acting compounds address multiple inflammatory pathways while potentially mitigating toxicity; and advanced drug delivery systems promise enhanced targeting to inflamed tissues (Wallace & Miller, 2020; Mohammad et al., 2024). As these innovations progress toward clinical translation, they may expand the therapeutic window of NSAIDs and improve outcomes for patients with autoimmune diseases.

Ultimately, rational NSAID prescribing requires individualized risk-benefit assessment, adherence to evidence-based guidelines, and integration within comprehensive disease management strategies centered on DMARD therapy. By optimizing NSAID use in this manner, clinicians can maximize symptomatic relief while minimizing harm in patients with autoimmune diseases.

References

Antman, E. M., Bennett, J. S., Daugherty, A., Furberg, C., Roberts, H., & Taubert, K. A. (2007). Use of nonsteroidal anti-inflammatory drugs: An update for clinicians: A scientific statement from the American Heart Association. *Circulation, 115*(12), 1634–1642. https://doi.org/10.1161/CIRCULATIONAHA.106.181424

Bally, M., Dendukuri, N., Rich, B., Nadeau, L., Helin-Salmivaara, A., Garbe, E., & Brophy, J. M. (2017). Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. *BMJ, 357*, j1909. https://doi.org/10.1136/bmj.j1909

Baviskar, P., Bedse, M., Sadique, S., Khandelwal, V., & Jain, D. (2025). Aceclofenac-loaded polymeric nanoparticles for transdermal delivery: Formulation optimization and anti-arthritic activity. *Journal of Drug Delivery Science and Technology, 103*, 106421. https://doi.org/10.1016/j.jddst.2024.106421

Bertolini, A., Ottani, A., & Sandrini, M. (2002). Dual acting anti-inflammatory drugs: A reappraisal. *Pharmacological Research, 46*(5), 381–385. https://doi.org/10.1016/s1043-6618(02)00218-0

Bindu, S., Mazumder, S., & Bandyopadhyay, U. (2020). Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochemical Pharmacology, 180*, 114147. https://doi.org/10.1016/j.bcp.2020.114147

Bourré-Tessier, J., & Haraoui, B. (2010). Methotrexate drug interactions in the treatment of rheumatoid arthritis: A systematic review. *Joint Bone Spine, 77*(4), 316–321. https://doi.org/10.1016/j.jbspin.2010.02.009

Bresalier, R. S., Sandler, R. S., Quan, H., Bolognese, J. A., Oxenius, B., Horgan, K., Lines, C., Riddell, R., Morton, D., Lanas, A., Konstam, M. A., & Baron, J. A. (2005). Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *New England Journal of Medicine, 352*(11), 1092–1102. https://doi.org/10.1056/NEJMoa050493

Capone, M. L., Tacconelli, S., Sciulli, M. G., Grana, M., Ricciotti, E., Minuz, P., Di Gregorio, P., Merciaro, G., Patrono, C., & Patrignani, P. (2005). Clinical pharmacology of platelet, monocyte, and vascular cyclooxygenase inhibition by naproxen and low-dose aspirin in healthy subjects. *Circulation, 111*(4), 469–475. https://doi.org/10.1161/01.CIR.0000153857.10569.FA

Cryer, B., & Feldman, M. (1998). Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *American Journal of Medicine, 104*(5), 413–421. https://doi.org/10.1016/s0002-9343(98)00091-7

De Vecchis, R., Baldi, C., & Biase, C. (2022). Cardiovascular and renal risks of NSAID use in patients with hypertension: A meta-analysis. *Journal of Clinical Medicine, 11*(15), 4389. https://doi.org/10.3390/jcm11154389

Derry, C. J., Derry, S., & Moore, R. A. (2017). Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews*, (5), CD001548. https://doi.org/10.1002/14651858.CD001548.pub2

Derry, S., Conaghan, P., Da Silva, J. A., Wiffen, P. J., & Moore, R. A. (2016). Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews*, (4), CD007400. https://doi.org/10.1002/14651858.CD007400.pub3

El Mansouri, L., Abourazzak, F., Harzy, T., Bensabbah, R., Hajjaj-Hassouni, N., & Allali, F. (2023). Moroccan recommendations for the management of spondyloarthritis. *Rheumatology International, 43*(2), 215–226. https://doi.org/10.1007/s00296-022-05245-9

Corresponding author: *Abouelhag H. A*
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doi: https://doi.org/10.33687/ricosbiol.04.04.117

El-Sayed, M. A., Abdel-Aziz, S. A., & El-Sayed, A. M. (2024). NSAIDs between past and present; a long journey towards an ideal COX-2 inhibitor lead. *RSC Advances, 14*(42), 30647–30661. https://doi.org/10.1039/d4ra04686b

Fanouriakis, A., Kostopoulou, M., Alunno, A., Aringer, M., Bajema, I., Boletis, J. N., Cervera, R., Doria, A., Gordon, C., Govoni, M., Houssiau, F., Jayne, D., Kouloumas, M., Kuhn, A., Larsen, J. L., Lerang, K., Moroni, G., Mosca, M., Schneider, M., … Boumpas, D. T. (2019). 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Annals of the Rheumatic Diseases, 78*(6), 736–745. https://doi.org/10.1136/annrheumdis-2019-215089

Farkouh, M. E., Greenberg, J. D., Jeger, R. V., Ramanathan, K., Verheugt, F. W., Chesebro, J. H., Kirshner, H., & Hochman, J. S. (2016). Cardiovascular outcomes with the use of nonsteroidal anti-inflammatory drugs in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases, 75*(6), 1043–1050. https://doi.org/10.1136/annrheumdis-2014-206825

Fiorucci, S., Santucci, L., & Morelli, A. (2003). 5-Aminosalicylic acid and its derivatives: A new class of nitric oxide-donating nonsteroidal anti-inflammatory drugs. *Drugs of Today, 39*(4), 275–284. https://doi.org/10.1358/dot.2003.39.4.799449

FitzGerald, G. A., & Patrono, C. (2001). The coxibs, selective inhibitors of cyclooxygenase-2. *New England Journal of Medicine, 345*(6), 433–442. https://doi.org/10.1056/NEJM200108093450607

FitzGerald, J. D., Dalbeth, N., Mikuls, T., Brignardello-Petersen, R., Guyatt, G., Abeles, A. M., Gelber, A. C., Harrold, L. R., Khanna, D., King, C., Levy, G., Libbey, C., Mount, D., Pillinger, M. H., Rosenthal, A., Singh, J. A., Sims, J. E., Smith, B. J., Wetherington, J. D., … Neogi, T. (2020). 2020 American College of Rheumatology guideline for the management of gout. *Arthritis Care & Research, 72*(6), 744–760. https://doi.org/10.1002/acr.24180

Flint, J., Panchal, S., Hurrell, A., van de Venne, M., Gayed, M., Schreiber, K., Arthanari, S., Cunningham, J., Flanders, L., Moore, L., Crossley, A., Purushotham, N., Desai, A., Piper, M., Nisar, M., Khamashta, M., Williams, D., Gordon, C., & Giles, I. (2016). BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: Standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology, 55*(9), 1693–1697. https://doi.org/10.1093/rheumatology/kew277

Gossec, L., Baraliakos, X., Kerschbaumer, A., de Wit, M., McInnes, I., Dougados, M., Primdahl, J., McGonagle, D. G., Aletaha, D., Balanescu, A., Balint, P. V., Bertheussen, H., Boehncke, W. H., Burmester, G. R., Cauli, A., de Vlam, K., Hellivell, P., Kavanaugh, A., Kvien, T. K., … Smolen, J. S. (2020). EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Annals of the Rheumatic Diseases, 79*(6), 700–712. https://doi.org/10.1136/annrheumdis-2020-217159

Grosser, T., Ricciotti, E., & FitzGerald, G. A. (2017). The cardiovascular pharmacology of nonsteroidal anti-inflammatory drugs. *Trends in Pharmacological Sciences, 38*(8), 733–748. *https://doi.org/10.1016/j.tips.2017.05.008*

Hammad, A., Mohammad, F., Niaz, N., Yunus, H., & Asim, A. (2024). Understanding the renal side effects of commonly prescribed drugs, such as NSAIDs, antibiotics, and chemotherapeutic agents, and strategies for prevention and management. *Bioanalysis Journal, 18*(2), 101–112. https://bioanalysisjournal.com/understanding-the-renal-side-effects-of-commonly-prescribed-drugs/

Harirforoosh, S., Asghar, W., & Jamali, F. (2013). Adverse effects of nonsteroidal antiinflammatory drugs: An update of gastrointestinal, cardiovascular and renal complications. *Journal of Pharmacy & Pharmaceutical Sciences, 16*(5), 821–847. *https://doi.org/10.18433/j3vw2f*

Ikdahl, E., Kerola, A., Sollerud, E., & Semb, A. G. (2024). Cardiovascular implications of non-steroidal anti-inflammatory drugs: A comprehensive review, with emphasis on patients with rheumatoid arthritis. *European Cardiology Review, 19*, e27. https://doi.org/10.15420/ecr.2024.24

Kato, S., Otsubo, R., & Yamada, Y. (2021). Topical NSAIDs for acute musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews*, (7), CD007402. *https://doi.org/10.1002/14651858.CD007402.pub4*

KDIGO. (2012). Chapter 2: Definition, identification, and prediction of CKD progression. *Kidney International Supplements, 3*(1), 63–72. *https://doi.org/10.1038/kisup.2012.64*

Kowalski, M. L., & Makowska, J. S. (2015). Seven steps to the diagnosis of NSAIDs hypersensitivity: How to use a basic algorithm. *Current Opinion in Allergy and Clinical Immunology, 15*(4), 331–337. https://doi.org/10.1097/ACI.0000000000000184

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2026, Vol. 4, No. 4, 25-35
doi: https://doi.org/10.33687/ricosbiol.04.04.117

Kowalski, M. L., Asero, R., Bavbek, S., Blanca, M., Blanca-Lopez, N., Bochenek, G., Brockow, K., Campo, P., Celik, G., Cernadas, J., Cortellini, G., Gomes, E., Niżankowska-Mogilnicka, E., Romano, A., Sanchez-Borges, M., Terreehorst, I., & Torres, M. J. (2013). Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy, 68*(10), 1219–1232. https://doi.org/10.1111/all.12260

Kulkarni, S. K., & Singh, V. P. (2008). Licofelone—A novel analgesic and anti-inflammatory agent. *Current Topics in Medicinal Chemistry, 8*(16), 1443–1455. https://doi.org/10.2174/156802608786264281

Lanas, A., García-Rodríguez, L. A., Polo-Tomás, M., Ponce, M., Alonso-Abreu, I., Perez-Aisa, M. A., Gonzalez, J. M., Bujanda, L., Castro, M., Pena, E., Herreros, B., & García, S. (2017). Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. *American Journal of Gastroenterology, 112*(6), 909–918. https://doi.org/10.1038/ajg.2017.52

Lanza, F. L., Chan, F. K., & Quigley, E. M. (2009). Guidelines for prevention of NSAID-related ulcer complications. *American Journal of Gastroenterology, 104*(3), 728–738. https://doi.org/10.1038/ajg.2009.115

Mahmood, A., Chaudhry, R., Moazam, M. M., Zahee, M. T., & Ullah, I. (2024). Comparative cardiovascular efficacy & safety of NSAIDs: A systematic review and meta-analysis of randomized controlled trials. *Journal of Advances in Medicine and Medical Research, 36*(5), 177–192. https://doi.org/10.9734/jammr/2024/v36i55427

Martel-Pelletier, J., Lajeunesse, D., Reboul, P., & Pelletier, J. P. (2003). Therapeutic role of dual inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs. *Annals of the Rheumatic Diseases, 62*(6), 501–509. https://doi.org/10.1136/ard.62.6.501

Mohammad, F., Alvi, S. B., & Khan, M. A. (2024). Design and evaluation of magnetic-targeted bilosomal gel for rheumatoid arthritis: Flurbiprofen delivery using superparamagnetic iron oxide nanoparticles. *Frontiers in Pharmacology, 15*, 1428365. https://doi.org/10.3389/fphar.2024.1428365

Mori, M., Takei, S., Shimizu, M., Yamasaki, Y., Yamazaki, K., & Yokota, S. (2024). Japan College of Rheumatology clinical practice guidelines for the management of juvenile idiopathic arthritis. *Modern Rheumatology, 34*(1), 1–15. https://doi.org/10.1093/mr/road089

Murray, M. D., & Brater, D. C. (1993). Renal toxicity of the nonsteroidal anti-inflammatory drugs. *Annual Review of Pharmacology and Toxicology, 33*, 435–465. https://doi.org/10.1146/annurev.pa.33.040193.002251

Onel, K. B., Horton, D. B., Lovell, D. J., Shenoi, S., Cuello, C. A., Angeles-Han, S. T., Becker, M. L., Cron, R. Q., Feldman, B. M., Ferguson, P. J., Gewanter, H., Guzman, J., Kimura, Y., Lee, T., Murphy, K., Nigrovic, P. A., Ombrello, M. J., Rabinovich, C. E., Rubin, M., … Ringold, S. (2022). 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: Therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. *Arthritis Care & Research, 74*(4), 521–537. https://doi.org/10.1002/acr.24853

Rani, A., Singh, S., & Kumar, A. (2025). Design, synthesis and in vitro evaluation of non-steroidal anti-inflammatory prodrugs for osteoarthritis. *Bioorganic Chemistry, 150*, 107630. https://doi.org/10.1016/j.bioorg.2025.107630

Ravelli, A., & Martini, A. (2007). Juvenile idiopathic arthritis. *The Lancet, 369*(9563), 767–778. https://doi.org/10.1016/S0140-6736(07)60363-1

Ricciotti, E., & FitzGerald, G. A. (2011). Prostaglandins and inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology, 31*(5), 986–1000. https://doi.org/10.1161/ATVBAHA.110.207449

Ricciotti, E., Dovizio, M., Di Francesco, L., Anzellotti, P., Salvatore, T., Di Francesco, A., Sciulli, M. G., & Patrignani, P. (2010). NCX 4040, a nitric oxide-donating aspirin, exerts anti-inflammatory effects through inhibition of I kappa B-alpha degradation in human monocytes. *Journal of Pharmacology and Experimental Therapeutics, 333*(2), 500–509. https://doi.org/10.1124/jpet.109.162107

Scarpignato, C., Lanas, A., Blandizzi, C., Lems, W. F., Hermann, M., & Hunt, R. H. (2015). Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis—An expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. *BMC Medicine, 13*, 55. https://doi.org/10.1186/s12916-015-0285-8

Scheiman, J. M. (2016). NSAID-induced gastrointestinal injury. *Journal of Clinical Gastroenterology, 50*(1), 5–10. https://doi.org/10.1097/MCG.0000000000000426

Silverstein, F. E., Faich, G., Goldstein, J. L., Simon, L. S., Pincus, T., Whelton, A., Makuch, R., Eisen, G., Agrawal, N. M., Stenson, W. F., Burr, A. M., Zhao, W. W., Kent, J. D., Lefkowith, J. B., Verburg, K. M., & Geis,

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RICOS BIOLOGY Journal
2026, Vol. 4, No. 4, 25-35
doi: https://doi.org/10.33687/ricosbiol.04.04.117

G. S. (2000). Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: The CLASS study: A randomized controlled trial. *JAMA, 284*(10), 1247–1255. https://doi.org/10.1001/jama.284.10.1247

Simon, L. S., Lanza, F. L., Lipsky, P. E., Hubbard, R. C., Talwalker, S., Schwartz, B. D., Isakson, P. C., & Geis, G. S. (1998). Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: Efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. *Arthritis & Rheumatism, 41*(9), 1591–1602. https://doi.org/10.1002/1529-0131(199809)41:9<1591::AID-ART9>3.0.CO;2-U

Singh, J. A., Saag, K. G., Bridges, S. L., Jr., Akl, E. A., Bannuru, R. R., Sullivan, M. C., Vaysbrot, E., McNaughton, C., Osani, M., Shmerling, R. H., Curtis, J. R., Furst, D. E., Parks, D., Kavanaugh, A., O'Dell, J., King, C., Leong, A., Matteson, E. L., Schousboe, J. T., … Tugwell, P. (2016). 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care & Research, 68*(1), 1–25. https://doi.org/10.1002/acr.22783

Smolen, J. S., Landewé, R. B. M., Bijlsma, J. W. J., Burmester, G. R., Dougados, M., Kerschbaumer, A., McInnes, I. B., Sepriano, A., van Vollenhoven, R. F., de Wit, M., Aletaha, D., Aringer, M., Askling, J., Balsa, A., Boers, M., den Broeder, A. A., Buch, M. H., Buttgereit, F., Caporali, R., … van der Heijde, D. (2020). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Annals of the Rheumatic Diseases, 79*(6), 685–699. https://doi.org/10.1136/annrheumdis-2019-216655

Stevenson, D. D., & Szczeklik, A. (2006). Clinical and pathologic perspectives on aspirin sensitivity and asthma. *Journal of Allergy and Clinical Immunology, 118*(4), 773–786. https://doi.org/10.1016/j.jaci.2006.07.024

Stouten, V., Westhovens, R., Pazmino, S., De Cock, D., Van der Elst, K., Joly, J., & Verschueren, P. (2019). Effectiveness of different combinations of DMARDs and glucocorticoid bridging in early rheumatoid arthritis: Two-year results of CareRA. *Rheumatology, 58*(12), 2284–2294. https://doi.org/10.1093/rheumatology/kez213

Trelle, S., Reichenbach, S., Wandel, S., Hildebrand, P., Tschannen, B., Villiger, P. M., Egger, M., & Jüni, P. (2011). Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta-analysis. *BMJ, 342*, c7086. https://doi.org/10.1136/bmj.c7086

van der Heijde, D., Ramiro, S., Landewé, R., Baraliakos, X., Van den Bosch, F., Sepriano, A., Regel, A., Ciurea, A., Dagfinrud, H., Dougados, M., van Gaalen, F., Géher, P., van der Horst-Bruinsma, I., Inman, R. D., Jongkees, M., Kiltz, U., Kvien, T. K., Machado, P. M., Marzo-Ortega, H., … Braun, J. (2017). 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Annals of the Rheumatic Diseases, 76*(6), 978–991. https://doi.org/10.1136/annrheumdis-2016-210770

Vane, J. R., & Botting, R. M. (1998). Mechanism of action of nonsteroidal anti-inflammatory drugs. *American Journal of Medicine, 104*(3A), 2S–8S. https://doi.org/10.1016/s0002-9343(97)00203-x

Wallace, J. L. (2008). Prostaglandins, NSAIDs, and gastric mucosal protection: Why doesn't the stomach digest itself? *Physiological Reviews, 88*(4), 1547–1565. https://doi.org/10.1152/physrev.00004.2008

Wallace, J. L., & Miller, M. J. (2020). Nitric oxide in the gastrointestinal tract: Opportunities for drug development. *British Journal of Pharmacology, 177*(12), 2653–2667. https://doi.org/10.1111/bph.14978

Wanders, A., Heijde, D., Landewé, R., Béhier, J. M., Calin, A., Olivieri, I., Zeidler, H., & Dougados, M. (2005). Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: A randomized clinical trial. *Arthritis & Rheumatism, 52*(6), 1756–1765. https://doi.org/10.1002/art.21035

Wang, M., Li, X. W., Yuan, S. C., Pan, J., Guo, Z. L., Sun, L. M., Jiang, S. Z., Zhao, M., Xue, W., Cai, H., Gu, L., Luo, D., Chen, L., Zhou, X. Q., Han, Q. Y., Li, J., Zhou, T., Xia, T., & Li, T. (2024). Indomethacin restrains cytoplasmic nucleic acid-stimulated immune responses by inhibiting the nuclear translocation of IRF3. *Journal of Molecular Cell Biology, 16*(4). https://doi.org/10.1093/jmcb/mjae018

Ward, M. M., Deodhar, A., Gensler, L. S., Dubreuil, M., Yu, D., Khan, M. A., Haroon, N., Borenstein, D., Wang, R., Biehl, A., Fang, M. A., Louie, G., Majithia, V., Ng, B., Bigham, R., Pianin, M., Shah, A. A., Sullivan, N., Turgunbaev, M., … Caplan, L. (2019). 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Care & Research, 71*(10), 1285–1299. https://doi.org/10.1002/acr.24025

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2026, Vol. 4, No. 4, 25-35
doi: https://doi.org/10.33687/ricosbiol.04.04.117

Warner, T. D., & Mitchell, J. A. (2004). Cyclooxygenases: New forms, new inhibitors, and lessons from the clinic. *FASEB Journal, 18*(7), 790–804. https://doi.org/10.1096/fj.03-0645rev

Warner, T. D., Giuliano, F., Vojnovic, I., Bukasa, A., Mitchell, J. A., & Vane, J. R. (1999). Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: A full in vitro analysis. *Proceedings of the National Academy of Sciences, 96*(13), 7563–7568. https://doi.org/10.1073/pnas.96.13.7563

Wehling, M. (2014). Non-steroidal anti-inflammatory drug use in chronic pain conditions with special emphasis on the elderly. *Zeitschrift für Rheumatologie, 73*(6), 521–528. https://doi.org/10.1007/s00393-013-1334-8

Whelton, A. (2000). Nephrotoxicity of nonsteroidal anti-inflammatory drugs: Physiologic foundations and clinical implications. *American Journal of Medicine, 109*(3), 13S–24S. https://doi.org/10.1016/s0002-9343(00)00594-6

Wirth, T., Lafforgue, P., & Pham, T. (2024). NSAID: Current limits to prescription. *Joint Bone Spine, 91*(4), 105685. https://doi.org/10.1016/j.jbspin.2023.105685

Zhang, X., Donahue, E. M., & Bourne, D. W. (2017). Drug interactions and NSAIDs. In *Nonsteroidal Anti-Inflammatory Drugs* (pp. 187–206). Springer. https://doi.org/10.1007/978-3-319-55053-2_9

Zhang, Y., Wang, S., Zhang, Y., & Chen, L. (2023). Neutrophil membrane-coated nanoparticles for targeted treatment of rheumatoid arthritis. *ACS Nano, 17*(5), 4567–4580. https://doi.org/10.1021/acsnano.2c10234

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Educational Notes

Basic Concepts in Immunology and Components of the Immune System

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Abstract

This chapter introduces the fundamental concepts of immunology, focusing on the relationship between infection and the host immune system. It defines key terms such as infection, pathogenicity, and normal microbiota, and classifies infections by localisation, incidence, etiology, and systematic site. The chapter then distinguishes between the two major branches of the immune system: nonspecific (innate) immunity and specific (adaptive) immunity. The cellular components—including lymphocytes (B cells, T cells, natural killer cells), mononuclear phagocytes, granulocytes, mast cells, and dendritic cells—are described in terms of their origin, maturation, and function. The primary lymphoid organs (bone marrow and thymus) and secondary lymphoid tissues (spleen, lymph nodes, and mucosa-associated lymphoid tissue) are explained as sites of lymphocyte development and antigen encounter. Finally, the physical and mechanical barriers that constitute the first line of defence—skin, mucous membranes, and associated secretions—are reviewed, with special attention to the role of M cells in mucosal immunity. Together, these elements provide the foundation for understanding how the body recognises and defends against microbial invaders while maintaining self-tolerance.

Keywords:
Infection, pathogenicity, normal microbiota, innate immunity, adaptive immunity, B lymphocytes, T lymphocytes, natural killer cells, macrophages, neutrophils, dendritic cells, thymus, bone marrow, spleen, lymph nodes, mucosal-associated lymphoid tissue (MALT), M cells, skin barrier, lysozyme, lactoferrin, first line of defence.

Learning Objectives

After studying this chapter, you should be able to:

1. Define infection, pathogenicity, and the normal microbiota.
2. Distinguish between nonspecific (innate) and specific (adaptive) immunity.
3. List the major cells of the immune system and describe their primary functions.
4. Identify the primary and secondary lymphoid organs and explain their roles.
5. Explain how physical and mechanical barriers contribute to first-line defense, including the role of M cells.

1. Infection and Disease

1.1 Definitions

- **Infection** – an interaction between a host and a microorganism that involves tissue damage (Abouelhag, 2010, p. 4).
- **Pathogenicity** – the ability of a microorganism to produce pathologic changes or disease.
- **Normal microbiota (normal flora)** – the mixture of microorganisms regularly found on skin and mucous membranes; they help prevent colonisation by pathogens (Wang et al., 2024).

1.2 Classification of Infection (Detailed Explanation)

Infections can be classified according to several criteria, each providing clinically useful information about the behaviour, spread, and impact of the infectious agent (Abouelhag, 2010, p. 4). The table below summarises the classification, followed by a detailed explanation of each category.

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Basis	Types
Localisation	Local, general (systemic), latent
Incidence	Sporadic, enzootic, epizootic
Etiology	Primary, secondary, mixed
Systematic (site)	Respiratory, urinary tract, etc.

A. Classification by Localisation (Site of Infection within the Body)

This refers to the anatomical distribution of the infection.

- **Local infection** – The microorganism remains confined to a single, well-defined area of the body. Examples include a boil (furuncle) on the skin or a localised abscess. The host's inflammatory response typically walls off the infection, preventing systemic spread (Murphy et al., 2022).
- **General (systemic) infection** – The microorganism spreads throughout the body via the bloodstream or lymphatic system. Bacteraemia (bacteria in blood) or septicaemia (systemic illness with fever, tachycardia, and petechial haemorrhages) are examples (Abouelhag, 2010, p. 5). Systemic infections often produce generalised signs such as fever, malaise, and lymphadenopathy.
- **Latent infection** – The microorganism remains dormant within the host for a prolonged period without producing detectable signs of disease. However, the immune system may still produce antibodies that can be detected by serological tests (Abouelhag, 2010, p. 4). Examples include herpesviruses (e.g., varicella-zoster virus) and *Mycobacterium tuberculosis*. Reactivation can occur when host immunity is compromised (Punt et al., 2023).

B. Classification by Incidence (Frequency and Pattern in a Population)

This classification describes how often and in what pattern an infection occurs within a host population.

- **Sporadic infection** – Isolated cases occur irregularly and unpredictably, with no clear pattern. For example, a single case of tetanus in a community is considered sporadic (Abouelhag, 2010, p. 4).
- **Enzootic infection** – A disease that recurs regularly (endemic) in a particular animal host population within a defined geographic area. For example, Lyme disease is enzootic in certain rodent and tick populations. The term is analogous to "endemic" in human epidemiology (Abbas et al., 2022).
- **Epizootic infection** – A disease suddenly affects a large number of animals in a population over a short period, then rapidly declines. This is analogous to an "epidemic" in humans. Examples include avian influenza outbreaks in poultry (Abouelhag, 2010, p. 4; Delves et al., 2023).

C. Classification by Etiology (Cause or Sequence of Infection)

This classification is based on the cause or the order in which different microorganisms contribute to disease.

- **Primary infection** – Caused by a single species of microorganism that initiates the disease process. For example, infection with *Mycobacterium tuberculosis* causing primary tuberculosis (Abouelhag, 2010, p. 4).
- **Secondary infection** – Occurs when a primary infection weakens the host's defences, allowing a different microorganism to cause an additional infection. For example, viral influenza (primary) may be followed by bacterial pneumonia caused by *Streptococcus pneumoniae* or *Staphylococcus aureus* (Abouelhag, 2010, p. 4).
- **Mixed infection** – Caused by more than one microorganism simultaneously, making diagnosis and treatment more difficult. For example, certain types of pneumonia may involve both bacteria and viruses, or a wound infection may contain multiple bacterial species (Abouelhag, 2010, p. 4; Wang et al., 2024).

D. Classification by Systematic Site (Anatomical System Affected)

This classification is based on the organ system involved. It is the most common clinical classification and guides both diagnosis and treatment.

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- **Respiratory tract infections** – Examples: common cold (rhinovirus), influenza, pneumonia, tuberculosis.
- **Urinary tract infections** – Examples: cystitis, pyelonephritis, often caused by *Escherichia coli*.
- **Gastrointestinal infections** – Examples: gastroenteritis (rotavirus, *Salmonella*), hepatitis.
- **Nervous system infections** – Examples: meningitis, encephalitis.
- **Skin and soft tissue infections** – Examples: cellulitis, impetigo, abscesses.
- **Cardiovascular infections** – Examples: endocarditis, sepsis.

(Murphy et al., 2022)

1.3 Transmission

- **Direct** – immediate contact, exhaled droplets, scales, discharge.
- **Indirect** – insects carry microorganisms mechanically.

1.4 Why Some Infections Spread More Easily

Factors that increase infectivity include airborne survival of the agent, susceptibility of body surfaces (e.g., respiratory tract > intact skin), large number and frequent release of microorganisms, and strain-specific communicability.

1.5 Host and Environmental Factors

- Immune status, age.
- Gender.
- General health.
- Population density.
- Sanitation level.

1.6 Special Terms

- **Bacteraemia** – microorganisms in blood/lymph.
- **Septicemia** – infection with systemic symptoms (fever, tachycardia, petechial haemorrhages).
- **Toxaemia** – toxins in the blood (e.g., tetanus).
- **Pyaemia** – pus circulating with multiple abscesses.

2. The Immune System: Overview

- **Immunity** (Latin *immunis* – free of burden) – the general ability to resist infection or disease.
- **Immunology** – the science that studies immune responses, including self/nonself discrimination (Science Immunology, 2025).

2.1 Two Types of Immune Responses

Feature	Nonspecific (Innate / Natural) Immunity	Specific (Adaptive) Immunity
Specificity	Broad (recognises general patterns)	Highly specific (recognises individual antigens)
Memory	None (same response each time)	Yes (improves on repeated exposure)
Response time	Immediate (minutes to hours)	Slower (days for primary response)
Main components	Physical barriers, phagocytes, complement, NK cells	B cells, T cells, antibodies

Both systems work together to eliminate pathogens (Murphy et al., 2022).

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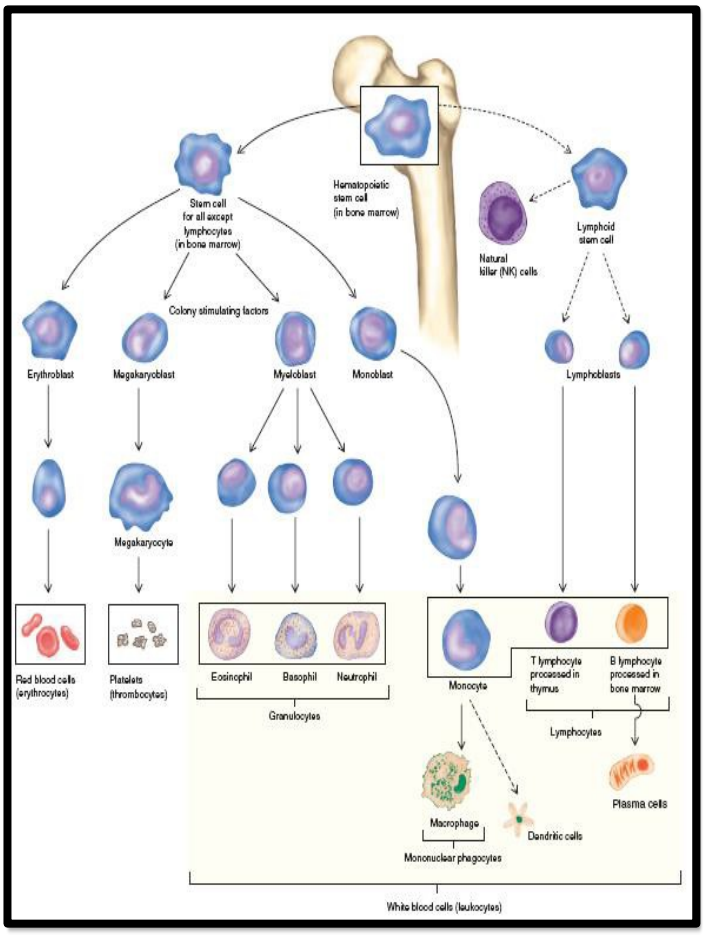
3. Cells of the Immune System

All leukocytes originate from **pluripotent haematopoietic stem cells** in fetal liver and bone marrow.



3.1 Lymphoid Cells (Major cells of specific immunity)

Cell Type	Maturation Site	Main Function
B cells	Bone marrow	Produce antibodies (plasma cells); present antigens
T cells	Thymus	Helper T cells (CD4+), cytotoxic T cells (CD8+), regulatory T cells
Natural Killer (NK) cells	Bone marrow	Kill virus-infected cells and tumour cells

(Abbas et al., 2022)

3.2 Mononuclear Phagocytes

- **Monocytes** – circulate in blood, then migrate into tissues and mature into macrophages.

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- **Macrophages** – highly phagocytic; act as antigen-presenting cells (APCs); have receptors for antibodies and complement (opsonisation).

3.3 Granulocytes (Polymorphonuclear Leukocytes – PMNs)

Type	Function
Neutrophils	Most abundant; primary phagocyte in acute inflammation; kill via lytic enzymes and reactive oxygen intermediates (Shafqat et al., 2023).
Eosinophils	Defend against parasites (helminths, protozoa); release cationic proteins.
Basophils	Non-phagocytic; release histamine and other mediators; involved in allergies (bind IgE).

3.4 Other Important Cells

- **Mast cells** – connective tissue; contain histamine granules; key in inflammation and hypersensitivity.
- **Dendritic cells** – most potent APCs; link innate and adaptive immunity by presenting antigens to T cells (Huang et al., 2023; Nature Portfolio, 2024).

4. Organs and Tissues of the Immune System

4.1 Primary Lymphoid Organs (where lymphocytes mature)

Organ/Tissue	Function
Bone marrow	Site of B-cell maturation; origin of all immune cells.
Thymus	Site of T-cell maturation (positive and negative selection).

(Delves et al., 2023)

4.2 Secondary Lymphoid Organs/Tissues (where antigen encounter occurs)

Organ/Tissue	Function
Spleen	Filters blood; traps blood-borne antigens.
Lymph nodes	Filter lymph; traps antigens from tissues.
Mucosa-associated lymphoid tissue (MALT)	Includes GALT (gut), BALT (bronchial), SALT (skin).

5. Physical and Mechanical Barriers (First Line of Defense)

5.1 Skin

- Thick outer layer of **keratin** (microbes cannot digest).
- Continuous shedding of epithelial cells.
- Dryness and mild acidity (pH 5–6) inhibit microbial growth.
- **Sebum** forms a protective film.
- Normal skin microbiota competes with pathogens.
- **Skin-associated lymphoid tissue (SALT)** – contains Langerhans cells (dendritic cells) and intraepidermal lymphocytes (T cells).

(Murphy et al., 2022)

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5.2 Mucous Membranes

Mucous membranes line the respiratory, digestive, and urogenital tracts. Mucus traps microorganisms, and secretions contain **lysozyme** (breaks bacterial cell walls), **lactoferrin** (binds iron), and **lactoperoxidase** (produces superoxide radicals). In addition to these chemical defences, the mucosal surface possesses specialised cells and lymphoid tissues that form an integrated immune barrier.

M Cells: Specialised Antigen-Sampling Cells

A key component of mucosal immunity is the **M cell (microfold cell)** . M cells are specialised epithelial cells found primarily in the **follicle-associated epithelium** of the **gut-associated lymphoid tissue (GALT)** , including Peyer's patches in the small intestine, as well as in the tonsils, adenoids, and bronchial-associated lymphoid tissue (BALT) (Murphy et al., 2022).

Unique structural features:

Unlike adjacent columnar epithelial cells, M cells lack a brush border (microvilli) on their apical surface. Instead, they have irregular **microfolds** that facilitate the adherence and uptake of luminal antigens. On their basolateral side, M cells possess a deep **intraepithelial pocket** that contains a dense cluster of lymphocytes (B cells, T cells) and macrophages (Punt et al., 2023).

Mechanism of antigen sampling:

M cells do not digest antigens for presentation. Instead, they act as **gatekeepers** that transport intact antigens (microbes, particles, soluble macromolecules) from the gut lumen to the underlying immune cells. The process involves:

1. **Adherence** – pathogens or particles bind to specific receptors (e.g., glycoprotein 2, integrins) on the M cell surface.
2. **Transcytosis** – the antigen is internalised and transported across the cell in endocytic vesicles.
3. **Release** – the antigen is discharged into the intraepithelial pocket, where it is immediately captured by resident dendritic cells or macrophages (Abbas et al., 2022; Nature Portfolio, 2024).

Immune consequences:

Once the antigen is delivered, dendritic cells (and some macrophages) process it and migrate to the lymphoid follicles. There, they present the antigen to naive B and T cells, initiating an **adaptive immune response**. B cells differentiate into IgA-secreting plasma cells, and the resulting **secretory IgA (sIgA)** is transported back across the epithelium into the lumen, where it neutralises pathogens and prevents their attachment (Wang et al., 2024; Delves et al., 2023).

Clinical relevance:

Some pathogens have evolved to exploit M cells as portals of entry. For example, *Salmonella typhi*, *Shigella flexneri*, and prions use M cell transcytosis to invade the host. Conversely, oral vaccines are designed to target M cells to induce effective mucosal immunity (Punt et al., 2023).

Mucosa-Associated Lymphoid Tissue (MALT)

The collection of M cells, underlying lymphoid follicles, and diffuse immune cells constitutes the mucosa-associated lymphoid tissue (MALT) . MALT can operate by two basic mechanisms:

- **Antigen sampling via M cells** leads to activation of B and T cells in organised lymphoid follicles.
- **Direct antigen contact** with dendritic cells that extend processes between epithelial cells can also occur.

Plasma cells derived from MALT follicles secrete **secretory IgA (sIgA)** , which is then transported into the lumen to neutralise specific antigens. (Wang et al., 2024)

5.3 Other Systems

- **Respiratory** – mucociliary blanket, alveolar macrophages, coughing/sneezing.
- **Gastrointestinal** – gastric acid (pH 2-3), pancreatic enzymes, bile, peristalsis, normal gut microbiota.
- **Genitourinary** – urine flushing, acidic vaginal environment (lactic acid from *Lactobacillus*).
- **Eye** – tears contain lysozyme, lactoferrin, and sIgA.

Summary

- The immune system comprises innate (nonspecific) and adaptive (specific) branches that cooperate to defend the host (Murphy et al., 2022).
- Key cellular players include B cells, T cells, NK cells, macrophages, neutrophils, and dendritic cells (Abbas et al., 2022; Punt et al., 2023).

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- Primary lymphoid organs (bone marrow, thymus) produce and mature lymphocytes; secondary organs (spleen, lymph nodes, MALT) are sites of antigen encounter and response initiation (Delves et al., 2023).
- Physical and mechanical barriers (skin, mucous membranes, secretions) form the first line of defence. Within mucous membranes, **M cells** play a critical role in sampling luminal antigens and initiating mucosal immune responses.

Review Questions

1. What is the difference between an infection and a disease?
2. Compare and contrast innate immunity with adaptive immunity.
3. List four types of granulocytes and their primary functions.
4. Why is the thymus considered a primary lymphoid organ?
5. Name three antimicrobial substances found in tears and mucus.
6. Describe the structure and function of M cells in mucosal immunity.

References

Abouelhag, H. (2010). Basic immunology, MLT 360: Hand out 2010/2011 [Unpublished course handout].

Abbas, A. K., Lichtman, A. H., & Pillai, S. (2022). *Cellular and molecular immunology* (10th ed.). Elsevier.

Delves, P. J., Martin, S. J., Burton, D. R., & Roitt, I. M. (2023). *Roitt's essential immunology* (14th ed.). Wiley-Blackwell.

Huang, Q., et al. (2023). Deciphering tumor-infiltrating dendritic cells in the single-cell era. *Experimental Hematology & Oncology, 12*(1), 45. https://doi.org/10.1186/s40164-023-00459-2

Murphy, K., Weaver, C., & Berg, L. (2022). *Janeway's immunobiology* (10th ed.). W.W. Norton & Company.

Nature Portfolio. (2024). Innate immunity. *Nature*. https://www.nature.com/subjects/innate-immunity

Punt, J., Stranford, S. A., Jones, P. P., & Owen, J. A. (2023). *Kuby immunology* (8th ed.). Macmillan Education.

Science Immunology. (2025). The multifunctional immune system. *Science*.

Shafqat, A., et al. (2023). How neutrophils shape the immune response: Reassessing their multifaceted role in health and disease. *International Journal of Molecular Sciences, 24*(24), 17583. https://doi.org/10.3390/ijms242417583

Wang, J., et al. (2024). Gut microbiota as a key regulator of intestinal mucosal immunity. *Life Sciences, 345*, 122612. https://doi.org/10.1016/j.lfs.2024.122612

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Data Availability Statement

No original datasets were generated for this review article. All cited data and findings are available within the original research publications referenced in the manuscript, accessible via the provided Digital Object Identifiers (DOIs) or through respective journal platforms.

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Educational Notes

Innate Immunity: Physical and Mechanical Barriers

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Abstract

Innate immunity constitutes the first line of host defense against invading pathogens (Turvey & Broide, 2010). Among its components, physical and mechanical barriers play a fundamental role by preventing microbial entry, colonization, and dissemination. This educational note provides a comprehensive overview of these barriers across different anatomical sites, including the skin, mucous membranes, respiratory tract, gastrointestinal tract, genitourinary tract, and eyes. It also details associated chemical factors (e.g., lysozyme, lactoferrin, gastric juice, bacteriocins) and cellular elements such as Langerhans cells, M cells, and alveolar macrophages (Abbas et al., 2020; Gallo & Hooper, 2012). The note emphasizes the synergistic action of physical, mechanical, and chemical mechanisms that together form an effective surveillance system. Understanding these barriers is essential for appreciating how the body resists infection before adaptive immunity is engaged.

Keywords:
: Innate immunity, physical barriers, mechanical barriers, skin, mucous membranes, lysozyme, lactoferrin, M cells, alveolar macrophages, SALT, mucosal-associated lymphoid tissue, antimicrobial peptides

Introduction to Innate Immunity

Innate immunity is the evolutionarily ancient, non-specific defense system that responds immediately to pathogens. Unlike adaptive immunity, it does not require prior exposure and lacks immunological memory (Turvey & Broide, 2010). The physical and mechanical barriers are the most external components of innate immunity, designed to **prevent pathogen entry** or **rapidly remove** them before infection can establish (Abbas et al., 2020).

These barriers include:

- Intact skin and mucous membranes.
- Mechanical actions such as shedding, flushing, ciliary movement, peristalsis, coughing, and sneezing.
- Chemical factors that directly kill or inhibit microbes (Gallo & Hooper, 2012).

Together, they provide a formidable first line of defense.

1. The Skin: A Multilayered Physical and Chemical Fortress

The skin is the largest organ of the body (≈1.5–2 m²) and serves as a primary physical barrier (Nestle et al., 2009).

1.1 Structural Features

- **Keratinocytes** form multiple layers of stratified squamous epithelium; the outer layer (stratum corneum) is composed of dead, keratin-filled cells that are impermeable to most microorganisms (Nestle et al., 2009).
- **Continuous shedding** of outer epithelial cells removes attached microbes (Abbas et al., 2020).
- **Relative dryness** (low water activity) slows microbial growth (Gallo & Hooper, 2012).
- **Mild acidity** (pH 5–6) – due to lactic acid, free fatty acids, and amino acids – inhibits many pathogenic bacteria and fungi (Schroder, 2011).
- **Sebum** (from sebaceous glands) contains triglycerides that are broken down into free fatty acids with antimicrobial activity (Schroder, 2011).
- **Normal skin microbiota** (e.g., *Staphylococcus epidermidis*) produces bacteriocins and competes for nutrients, antagonizing pathogens like *Staphylococcus aureus* (Gallo & Hooper, 2012).
- **Hygiene** (washing) mechanically removes transient microorganisms.

1.2 Skin-Associated Lymphoid Tissue (SALT)

The skin is not just a passive barrier; it contains specialized immune cells (Nestle et al., 2009):

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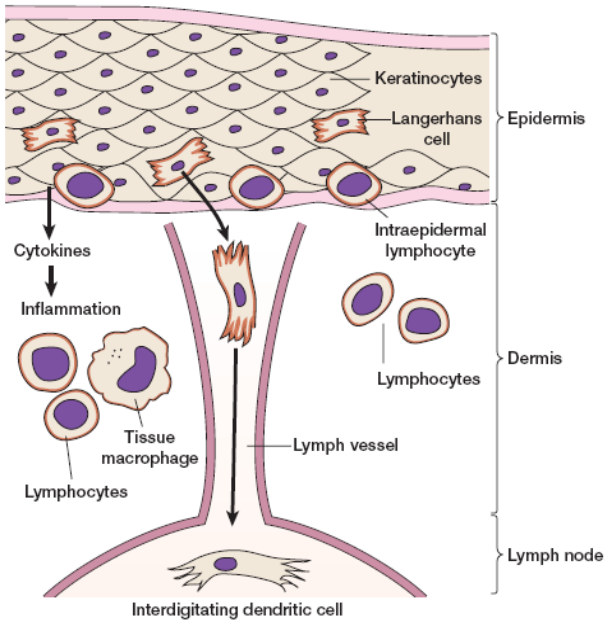
- **Langerhans cells** – dendritic cells in the epidermis that phagocytose antigens, migrate to draining lymph nodes, mature into interdigitating dendritic cells, and present antigens to naïve T cells, initiating adaptive immunity (Abbas et al., 2020).
- **Intraepidermal lymphocytes** – primarily γδ T cells that act like cytotoxic T lymphocytes, destroying infected keratinocytes (Nestle et al., 2009).
- **Large numbers of macrophages** in the dermis that phagocytose pathogens and produce inflammatory cytokines (Abbas et al., 2020).



2. Mucous Membranes and Mucosal-Associated Lymphoid Tissue (MALT)

Mucous membranes line internal cavities exposed to the external environment (oral cavity, nasal passages, gut, vagina, etc.). They are more delicate than skin but have specialized defenses (Mestecky et al., 2015).

2.1 General Features

- **Mucus** – a viscous secretion containing glycoproteins (mucins) that traps microorganisms (Mestecky et al., 2015).
- **Antimicrobial components**:
  - **Cervical mucus** – impedes ascent of bacteria into the uterus.
  - **Prostatic fluid** – contains zinc and antibacterial factors.
  - **Tears** – contain lysozyme, lactoferrin, and sIgA (Kolar & McDermott, 2019).

2.2 M Cells (Microfold Cells)

M cells are specialized epithelial cells found overlying lymphoid follicles in the gut, tonsils, and Peyer's patches (Mestecky et al., 2015).

- **Structure**: Lack microvilli (brush border) but have a pocket on their basolateral side containing B cells, T cells, and macrophages (Abbas et al., 2020).
- **Function**:

1. Phagocytose antigens and pathogens from the gut lumen.
2. Transport them across the epithelial barrier into the pocket.
3. Macrophages in the pocket engulf the antigen.
4. Alternatively, M cells deliver antigens to organized lymphoid follicles.
5. B cells in the follicle recognize the antigen, mature into plasma cells, and secrete **secretory IgA (sIgA)** (Mestecky et al., 2015).
6. sIgA is transported into the gut lumen to neutralize specific pathogens.

This mechanism is a critical bridge between innate and adaptive immunity at mucosal surfaces (Abbas et al., 2020).

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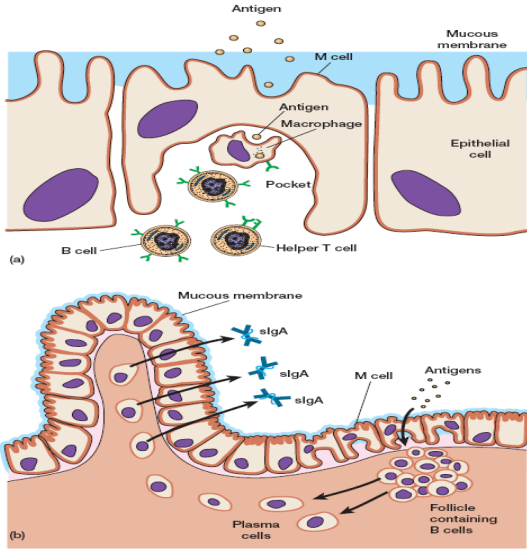

3. Defenses of the Respiratory System

The respiratory tract is constantly exposed to airborne pathogens and particulates. Multiple barriers protect it (Sarkar & Tindle, 2021).

3.1 Upper Respiratory Tract

- **Nasal cilia** beat toward the pharynx, moving mucus (with trapped microbes) to the mouth for swallowing or expulsion (Abbas et al., 2020).
- **Humidification** of inhaled air causes hygroscopic (water-absorbing) microorganisms to swell, which may disrupt their membranes and also facilitates phagocytosis.
- **Mucociliary blanket** – a layer of mucus on ciliated epithelial cells that traps particles <10 μm in diameter (including most bacteria and viruses). Cilia beat at ≈1000 beats/min to propel mucus upward (Sarkar & Tindle, 2021).

3.2 Reflexes

- **Coughing** and **sneezing** reflexively expel large amounts of air and mucus, removing irritants and pathogens (Abbas et al., 2020).

3.3 Saliva

Saliva from the mouth washes microorganisms from the oral and nasopharyngeal areas into the stomach, where gastric acid destroys them (Gallo & Hooper, 2012).

3.4 Lower Respiratory Tract and Alveolar Macrophages

- **Alveolar macrophages** reside in the lung alveoli. They are highly phagocytic and can ingest and kill most bacteria via reactive oxygen species and lysosomal enzymes. They also clear apoptotic cells and debris (Sarkar & Tindle, 2021).
- In addition, **surfactant proteins** (SP-A and SP-D) act as opsonins that enhance phagocytosis (Abbas et al., 2020).

4. Gastrointestinal Tract Defenses

The GI tract faces a high microbial load from ingested food and water. Its defenses are both physical and chemical (Gallo & Hooper, 2012).

4.1 Chemical Barriers

- **Gastric juice** (pH 1.5–3.5) – destroys most ingested bacteria, parasites, and viruses. Only a few pathogens (e.g., *Helicobacter pylori*, *Vibrio cholerae*) survive (Abbas et al., 2020).
- **Pancreatic enzymes** (trypsin, chymotrypsin) – digest bacterial cell walls and proteins.
- **Bile** – contains bile salts that disrupt bacterial membranes (Gallo & Hooper, 2012).

4.2 Mechanical Defenses

- **Peristaltic movement** – propels intestinal contents forward, preventing stasis and colonization (Abbas et al., 2020).
- **Intestinal microbiota** (commensal bacteria) – provide colonization resistance via:

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- Production of **bacteriocins** (e.g., colicin from *E. coli*, staphylococcin from *Staphylococcus*) (Gallo & Hooper, 2012).
- Competition for nutrients and adhesion sites.
- Stimulation of host immune responses (Mestecky et al., 2015).

5. Genitourinary Tract Defenses

The urinary and reproductive tracts are protected by several features (Abbas et al., 2020):

- **Urine properties**: Low pH (≈5.5–6.5), high urea concentration, uric acid, and hippuric acid – all inhibit microbial growth.
- **Hypotonic effect** of the kidney medulla – creates osmotic stress for bacteria.
- **Flushing action** – frequent voiding of urine mechanically removes pathogens.
- **Distance barrier** – long urethra (≈20 cm in males) makes ascending infection more difficult.
- **Secretory antibodies (sIgA)** in cervical mucus neutralize sperm-borne and sexually transmitted pathogens (Mestecky et al., 2015).
- **Prostatic antibacterial factor** – a zinc-containing peptide with antimicrobial activity.

6. The Eyes: Continuous Cleansing

The ocular surface is constantly exposed but remains remarkably infection-free due to (Kolar & McDermott, 2019):

- **Continuous flushing** by tears (produced by lacrimal glands, drained via nasolacrimal duct).
- **Tear composition**:
  - **Lysozyme** (muramidase) – breaks the β(1→4) bond between N-acetylmuramic acid and N-acetylglucosamine in peptidoglycan, especially effective against Gram-positive bacteria (Kolar & McDermott, 2019).
  - **Lactoferrin** – iron-binding protein that sequesters iron, limiting bacterial growth (Kolar & McDermott, 2019).
  - **sIgA** – neutralizes pathogens and prevents adhesion (Mestecky et al., 2015).
  - **Lactoperoxidase** – generates superoxide radicals that kill microbes.

Thus, tears provide both physical (flushing) and chemical protection.

7. Chemical Barriers: A Closer Look

While many chemical factors are associated with specific sites, some are systemic or widely distributed (Gallo & Hooper, 2012; Schroder, 2011).

Chemical Barrier	Source	Mechanism of Action
Lysozyme	Tears, saliva, mucus, milk	Hydrolyzes peptidoglycan (Gram-positive bacteria) (Kolar & McDermott, 2019)
Lactoferrin	Neutrophils, macrophages, secretions	Iron chelation; disrupts bacterial membranes (Kolar & McDermott, 2019)
Lactoperoxidase	Saliva, milk, tears	Generates hypothiocyanite and superoxide radicals
Gastric juice	Stomach	Acid denaturation of proteins (Abbas et al., 2020)
Salivary glycoproteins	Saliva	Inhibit bacterial adhesion
Urea	Urine	Alkaline degradation products are antimicrobial
Bacteriocins (colicin, staphylococcin)	Commensal bacteria	Pore formation, cell wall synthesis inhibition (Gallo & Hooper, 2012)
β-Lysin	Blood platelets	Disrupts microbial plasma membrane
Leukins	Neutrophils	Cationic antimicrobial peptides (Schroder, 2011)
Phagocytin	Phagocytes	Antimicrobial protein
Prostatic antibacterial factor	Prostate fluid	Zinc-dependent antimicrobial activity

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8. Summary and Clinical Relevance

- Physical and mechanical barriers are the first and most immediate components of innate immunity (Turvey & Broide, 2010).
- They act by **blocking entry** (skin, mucous membranes), **removing microbes** (shedding, cilia, flushing, peristalsis), and **killing** (chemicals, phagocytes) (Abbas et al., 2020).
- These barriers are not passive; they include specialized immune cells (Langerhans cells, M cells, alveolar macrophages) that initiate adaptive responses when breached (Nestle et al., 2009; Sarkar & Tindle, 2021).
- **Defects in these barriers** predispose to infection: e.g., burns (loss of skin barrier), cystic fibrosis (impaired mucociliary clearance), gastric acid suppression (increased risk of GI infections) (Gallo & Hooper, 2012).

Understanding these mechanisms is crucial for developing strategies to prevent infections and for appreciating how the body maintains homeostasis with the microbial world.

References

Abbas, A. K., Lichtman, A. H., & Pillai, S. (2020). *Cellular and molecular immunology* (10th ed.). Elsevier. [ISBN: 978-0323524577]

Gallo, R. L., & Hooper, L. V. (2012). Epithelial antimicrobial defence of the skin and intestine. *Nature Reviews Immunology*, 12(7), 503–516. https://doi.org/10.1038/nri3228

Kolar, S. S., & McDermott, A. M. (2019). Role of lactoferrin in the eye. *Biometals*, 32(3), 365–374. https://doi.org/10.1007/s10534-019-00193-1

Mestecky, J., Strober, W., Russell, M. W., Kelsall, B. L., Cheroutre, H., & Lambrecht, B. N. (Eds.). (2015). *Mucosal immunology* (4th ed.). Academic Press. https://doi.org/10.1016/C2012-0-00539-1

Nestle, F. O., Di Meglio, P., Qin, J. Z., & Nickoloff, B. J. (2009). Skin immune sentinels in health and disease. *Nature Reviews Immunology*, 9(10), 679–691. https://doi.org/10.1038/nri2622

Sarkar, A., & Tindle, C. (2021). Alveolar macrophages in lung inflammation and resolution. *Frontiers in Immunology*, 12, 758789. https://doi.org/10.3389/fimmu.2021.758789

Schroder, J. M. (2011). Antimicrobial peptides in the skin. *Seminars in Immunopathology*, 33(1), 3–13. https://doi.org/10.1007/s00281-010-0210-5

Turvey, S. E., & Broide, D. H. (2010). Innate immunity. *Journal of Allergy and Clinical Immunology*, 125(2 Suppl 2), S24–S32. https://doi.org/10.1016/j.jaci.2009.07.016

Data Availability Statement

No original datasets were generated for this review article. All cited data and findings are available within the original research publications referenced in the manuscript, accessible via the provided Digital Object Identifiers (DOIs) or through respective journal platforms.

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