Manganese Metabolism in Lyme Disease Pathogenesis and Therapeutic Implications: From Current Therapy to AI-Directed Drug Discovery

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Abstract

This review synthesizes current understanding of bacterial manganese metabolism as a therapeutic target, with specific focus on *Borrelia burgdorferi*, the causative agent of Lyme disease. We examine the pathogen's unique manganese-dependent biology, current standard-of-care treatments, and emerging research directions including transporter inhibition, metal homeostasis disruption, and AI-accelerated drug design. The analysis reveals multiple validated attack surfaces for developing narrow-spectrum, resistance-resistant antibiotics.

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1 Introduction: Manganese as an Antimicrobial Target

Manganese (Mn) metabolism represents a promising but underexplored avenue for antibiotic development. Despite its potential, **no currently licensed antibiotics specifically manipulate bacterial manganese use as their primary mechanism of action**. However, several experimental strategies exploit manganese pathways, with particular promise against pathogens that have evolved iron-independent, manganese-centric metabolisms.

1.1 Research Context: Manganese in Antimicrobial Development

This report was developed in response to a Hacker News discussion on November 15, 2025 [1] regarding recent findings by Hoffman and Daly at Northwestern University [2]. Their research characterizes manganese as a "double-edged sword" in Lyme disease, demonstrating that *Borrelia burgdorferi* simultaneously depends on and is vulnerable to manganese homeostasis disruption. The publication sparked significant online discourse about potential therapeutic approaches exploiting this metabolic vulnerability.

While no currently licensed antibiotics specifically target bacterial manganese metabolism, several pathogens—including *Borrelia burgdorferi*—exhibit unique manganese dependencies that present therapeutic opportunities. Understanding these metal-homeostasis pathways may enable development of narrow-spectrum antimicrobials with reduced resistance potential.

2 *Borrelia burgdorferi*: A Uniquely Manganese-Dependent Pathogen

Borrelia burgdorferi, the spirochete causing Lyme disease, possesses an exceptionally manganese-dependent metabolism that distinguishes it from most bacterial pathogens. The organism has eliminated iron from its proteome entirely, making manganese its critical transition metal cofactor for survival and pathogenesis.

2.1 Manganese Acquisition and Essential Systems

2.1.1 BmtA: The Sole Manganese Transporter

The bacterium's only manganese transporter is **BmtA (BB0219)**, a protein lacking homology to known bacterial Mn transporters. BmtA is:

- Essential for virulence in both mammalian and tick hosts [3]
- Required for intracellular manganese accumulation [3]
- Critical for resistance to oxidative stress [3]

BmtA mutants exhibit severely reduced intracellular manganese, impaired growth, and heightened sensitivity to EDTA chelation and oxidative damage.

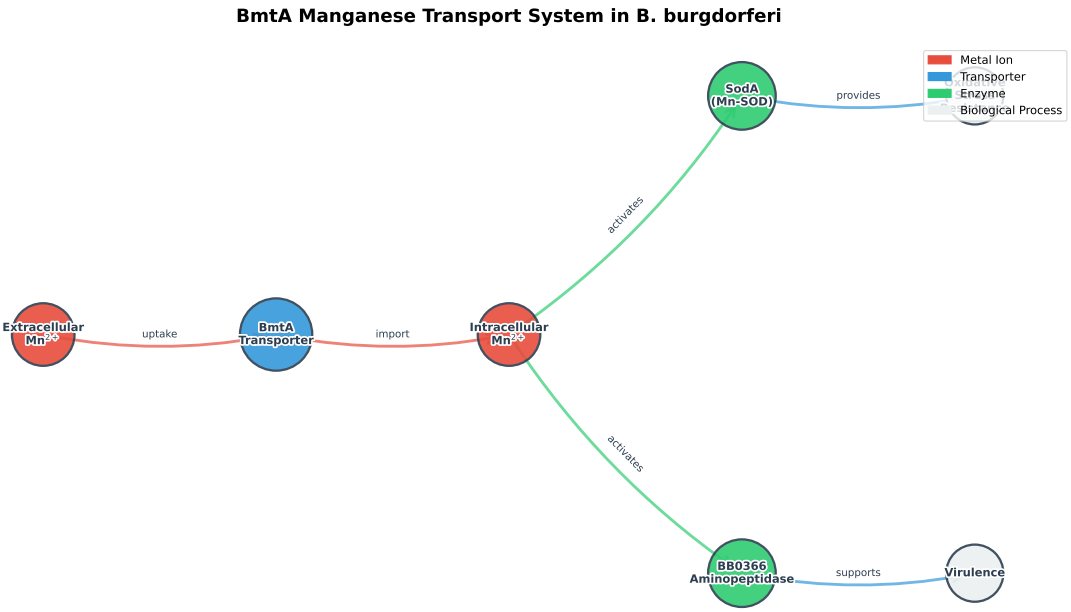

Figure 1: *BmtA manganese transport system in Borrelia burgdorferi. The BmtA transporter is essential for importing extracellular Mn^{2+}, which activates critical enzymes including SodA (manganese-dependent superoxide dismutase) and BB0366 aminopeptidase, providing oxidative stress resistance and supporting virulence.*

2.1.2 Manganese-Dependent Enzymes

- **Superoxide Dismutase (SodA)**: The primary antioxidant defense is a manganese-dependent SOD identified in *B. burgdorferi* [4].
- **Metalloproteases**: Additional enzymes including the BB0366 aminopeptidase require manganese activation [5].

2.2 Anomalous Metal Homeostasis

Unlike typical bacteria, *B. burgdorferi* **accumulates remarkably high intracellular manganese while maintaining near-zero iron concentrations**. This adaptation is essential for SodA activity and survival in the manganese-rich, iron-poor environments of its hosts [6, 7].

2.3 Host-Pathogen Metal Competition

The host immune system naturally exploits manganese dependence through nutritional immunity:

- **Calprotectin**: Produced by neutrophils, this protein sequesters nutrient metals including manganese in the infection microenvironment, inhibiting bacterial superoxide defense [8].

This metal restriction weakens pathogens and enhances susceptibility to immune-mediated killing.

2.4 Therapeutic Vulnerabilities

The pathogen's dependence on precise manganese homeostasis represents a therapeutic vulnerability. Both manganese deprivation (through BmtA inhibition) and potential disruption of manganese-dependent enzymes could serve as attack surfaces for novel antimicrobials targeting this unique metabolic pathway.

3 Current Standard Therapy for Lyme Disease

Treatment guidelines follow the 2020 IDSA/AAN/ACR recommendations, with CDC and Mayo Clinic updates through 2025 [9, 10].

3.1 Early Localized Disease (Erythema Migrans)

First-line oral antibiotics for 7–14 days:

- **Doxycycline**: 100 mg twice daily (adults)
- **Amoxicillin**: 500 mg three times daily (adults) or 50 mg/kg/day in 3 doses (children)
- **Cefuroxime axetil**: 500 mg twice daily (adults) or 30 mg/kg/day in 2 doses (children)

Single-dose doxycycline prophylaxis has been shown effective for prevention after tick bite [11].

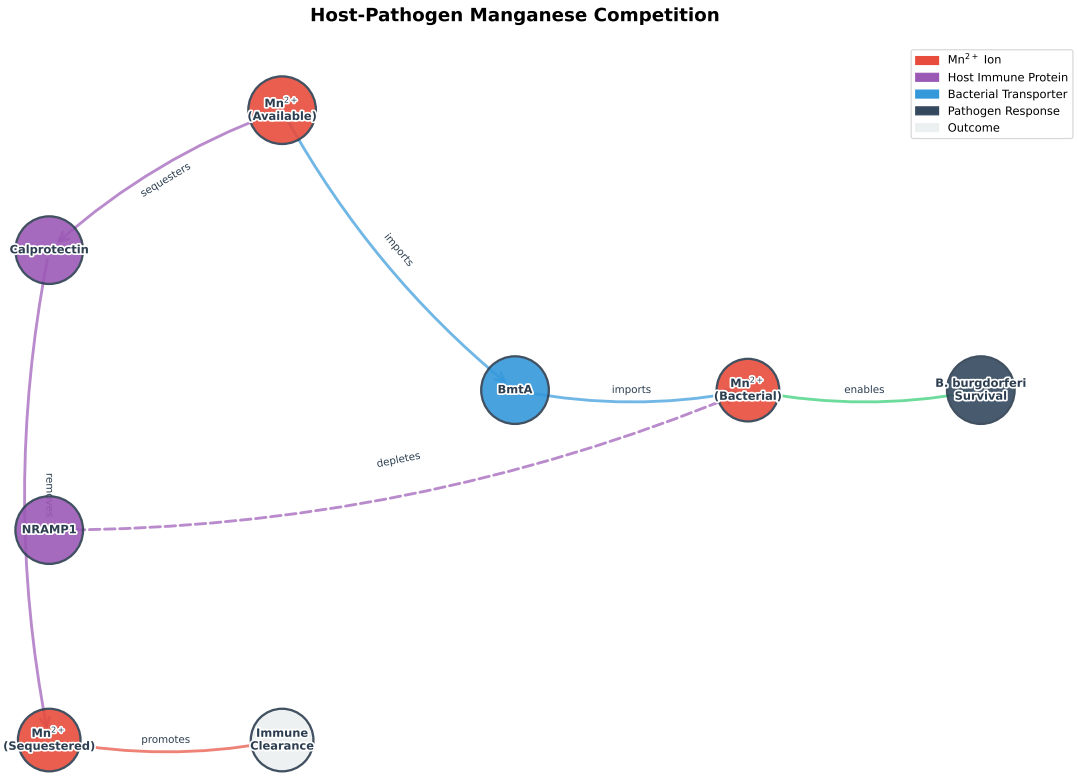

Figure 2: *Host-pathogen manganese competition in Lyme disease. The host immune system employs calprotectin to sequester available Mn^{2+} and NRAMP1 to deplete intracellular manganese from phagosomes, competing directly with bacterial BmtA transport. Successful manganese acquisition by B. burgdorferi enables survival, while effective host sequestration promotes immune clearance.*

3.2 Early Disseminated Disease

3.2.1 Neurologic Manifestations

- Meningitis, cranial nerve palsy, radiculoneuropathy: Oral doxycycline 100 mg twice daily for 14–21 days
- Severe neuroborreliosis (encephalitis, myelitis): IV ceftriaxone 2 g once daily for 14–28 days [12]

3.2.2 Cardiac Manifestations

- Mild carditis (first-degree AV block <300 ms): Oral regimen for 14–21 days
- Severe carditis (high-degree AV block): IV ceftriaxone 2 g once daily for 14–21 days [13]

3.3 Late Disease

3.3.1 Lyme Arthritis

- Initial: Oral antibiotics for 28 days

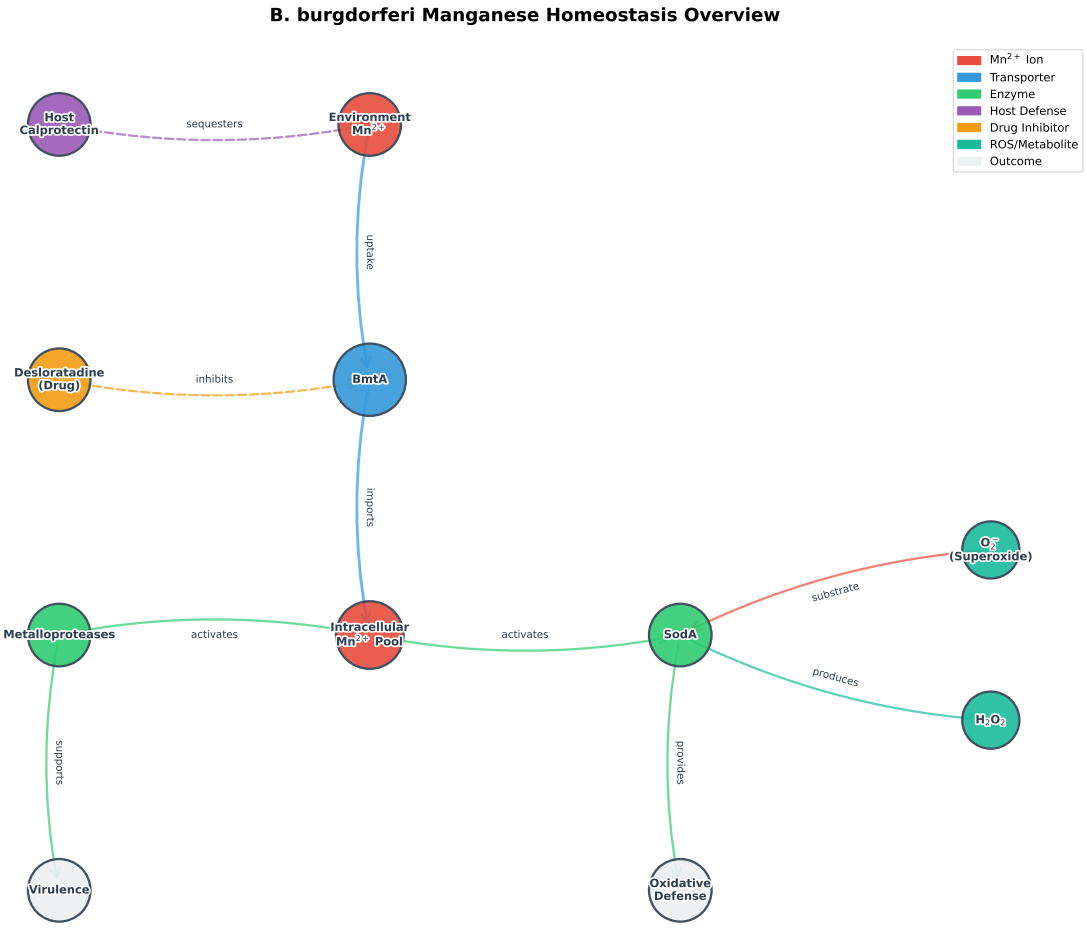

Figure 3: *Comprehensive overview of B. burgdorferi manganese homeostasis. This integrated pathway shows the interplay between environmental manganese availability, host immune sequestration (calprotectin), bacterial import (BmtA), manganese-dependent enzyme activation (SodA, metalloproteases), oxidative defense, and therapeutic intervention points (desloratadine inhibition).*

- Refractory/recurrent: Second 28-day oral course (different agent) or IV ceftriaxone for 2–4 weeks
- **Persistent arthritis after antibiotics**: Treat as post-infectious/autoimmune with NSAIDs/hydroxychloroquine; no further antibiotics [14]

3.3.2 Acrodermatitis Chronica Atrophicans

Oral doxycycline, amoxicillin, or cefuroxime for 21–28 days [15].

3.4 Post-Exposure Prophylaxis

Single-dose doxycycline (200 mg adult, 4.4 mg/kg children $\geq$ 8 years) within 72 hours of tick removal *only if*:

- Tick is identified as *Ixodes* species

- Attached ≥36 hours
- Tick from highly endemic area [16]

3.5 Special Populations

- **Pregnancy**: Amoxicillin preferred; avoid doxycycline
- **Children <8 years**: Amoxicillin or cefuroxime; doxycycline acceptable for short courses if indicated
- **Hospitalized patients**: Start IV ceftriaxone until clinical improvement, then transition to oral therapy

Key principles: Oral therapy is preferred when equivalent in efficacy, macrolides (azithromycin) are second-line due to lower efficacy, and prolonged antibiotics >28 days show no proven benefit for post-treatment Lyme disease syndrome [17].

4 Research Directions for Novel Therapeutics

4.1 BmtA Transporter Inhibition: A Validated Attack Surface

Immediate Priority: Optimize BmtA inhibitors discovered through virtual screening.

- **Lead Compound Optimization**: Build on desloratadine's demonstrated borreliacidal activity through BmtA binding and manganese transport inhibition [18]:
  - Structure-activity relationship studies to improve affinity while reducing antihistamine off-target effects
  - Prodrug design to enhance bioavailability and CNS penetration for neuroborreliosis
  - Evaluation of related tricyclic compounds (loratadine, 3-hydroxydesloratadine)
- **Mechanism Studies**: Use structural biology approaches to solve BmtA structure with bound inhibitors, enabling rational drug design
- **Host Safety Assessment**: Evaluate whether BmtA inhibitors affect mammalian Mn transporters (ZIP8, ZIP14, DMT1) to ensure specificity and safety

4.2 Manganese Homeostasis Disruption

Innovative Approach: Exploit the critical dependence on manganese balance.

- **Dual Inhibition**: Combine BmtA blockade with Mn-dependent enzyme inhibitors (e.g., SodA inhibitors) to create synergistic oxidative stress and disrupt manganese-dependent metabolism.
- **Host Immune Augmentation**: Develop approaches that enhance the natural host defense mechanisms of manganese sequestration through calprotectin and NRAMP1 [8].

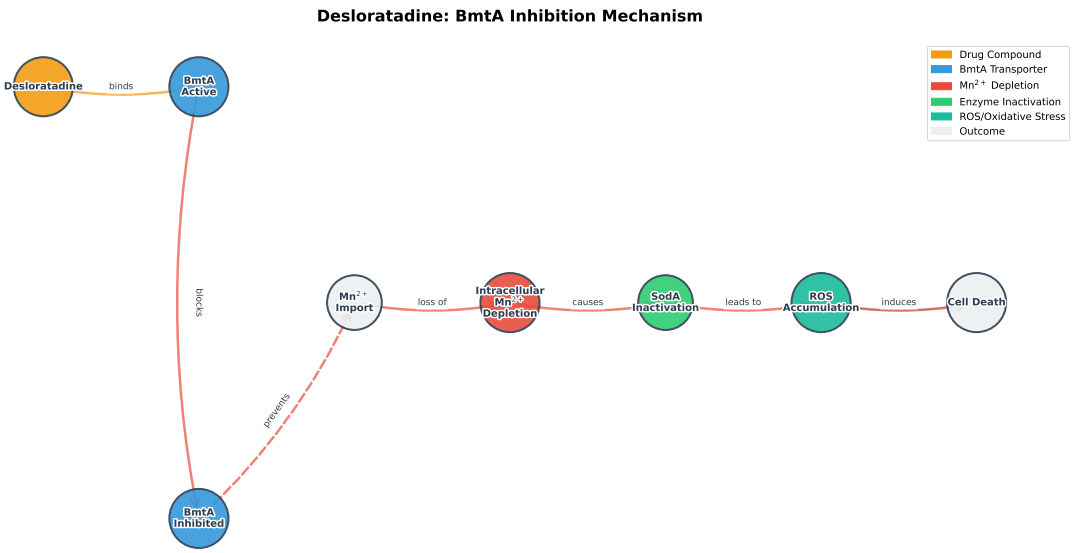

Figure 4: *Mechanism of BmtA inhibition by desloratadine. The antihistamine drug binds to BmtA, blocking manganese import and leading to intracellular Mn^{2+} depletion. This inactivates the manganese-dependent superoxide dismutase (SodA), causing reactive oxygen species (ROS) accumulation and ultimately bacterial cell death.*

4.3 Metabolic Modeling-Guided Target Discovery

Computational Pipeline: Expand the genome-scale metabolic model (iBB151) to identify species-specific vulnerabilities beyond manganese metabolism [19].

- **Prioritize 28 Narrow-Spectrum Targets**: Focus on the 21 reactions essential only in *B. burgdorferi*:
  - Pyridoxal kinase (confirmed lethal at 0.5 mg/mL with pemetrexed)
  - Serine hydroxymethyltransferase (confirmed lethal at 1.0 mg/mL with theophylline)
  - Mevalonate pathway enzymes (8 reactions) - unique among bacteria
- **Drug Repurposing**: Screen the 21 species-specific targets against FDA-approved drug libraries, as successfully done for BmtA.
- **Tick Stage Metabolism**: Model metabolic differences between spirochete forms in tick vectors vs. mammalian hosts to identify stage-specific targets

4.4 AlphaFold-Assisted Drug Design

Recent advances in AI-powered protein structure prediction offer transformative potential for accelerating discoveries against validated targets.

4.4.1 AlphaFold Applications in Lyme Disease Research

- **FtsH Protease (BB0789) Structure Prediction**: AlphaFold successfully predicted the missing structural details in the central pore loop region of the BB0789 hexameric protease, complementing crystallographic data and providing a complete

functional model [20]. This enzyme is crucial for *B. burgdorferi* infectivity in both mouse and tick hosts.

- **Limitations and Improvements**: A 2022 MIT study found that existing molecular docking simulations using AlphaFold structures performed only marginally better than chance for predicting protein-drug interactions. However, machine-learning refinement improved performance, indicating that AlphaFold predictions must be coupled with additional modeling advances for effective drug discovery [21].

- **AlphaFold 3 Enhancements**: The latest version predicts interactions with DNA, RNA, and small molecules with up to 50% greater accuracy than traditional methods. Isomorphic Labs has demonstrated success designing small molecules that bind tightly to predicted pockets, as shown in the TIM-3 cancer immunotherapy case study [22].

4.4.2 Specific AlphaFold-Directed Research Directions

1. **BmtA Structure Prediction and Inhibitor Design**: Since no experimental BmtA structure exists, AlphaFold could generate a high-confidence model to enable:
   - Structure-based virtual screening of compound libraries
   - Rational optimization of desloratadine analogs
   - Prediction of the transport mechanism to identify allosteric inhibition sites
2. **Manganese-Dependent Enzyme Targeting**: AlphaFold structures of SodA and BB0366 aminopeptidase would enable:
   - Identification of Mn-binding site inhibitors
   - Design of metal-chelating molecules that specifically target bacterial enzymes over human homologs
   - Structure-activity relationship studies without requiring initial crystallization
3. **Protein-Protein Interface Disruption**: AlphaFold 3's improved accuracy in predicting protein complexes could help design:
   - Molecules that disrupt BmtA oligomerization (if it forms multimers)
   - Inhibitors of essential protein complexes in the mevalonate pathway
   - Therapeutic antibodies that target surface-exposed manganese-binding proteins
4. **Off-Target Prediction**: AlphaFold models of human Mn transporters (ZIP8, ZIP14, DMT1) could be used in silico to screen for selective toxicity *before* animal studies.

4.4.3 Challenges and Validation Requirements

- **Accuracy Variability**: AlphaFold 3 success rates range from 40-80% depending on interaction type, with particular difficulty in protein-RNA complexes [23]

- **Hallucination Risk**: Diffusion-based architectures can generate plausible but non-existent molecular structures, requiring experimental verification [23]
- **Validation Pipeline**: Any AlphaFold-predicted target requires:
  - Experimental structure determination for lead compounds
  - Isothermal titration calorimetry to verify binding
  - Whole-cell activity assays under manganese-limited and -replete conditions

5 Clinical Development Priorities

5.1 Strategic Trial Design

Focus on unmet medical needs where manganese-targeting offers clear advantages:

- **Acute Prophylaxis**: BmtA inhibitors for single-dose prophylaxis after tick bites (alternative to doxycycline)
- **Neuroborreliosis**: CNS-penetrant Mn metabolism disruptors for CNS infections where current antibiotics have poor efficacy
- **Post-Treatment Lyme Disease Syndrome (PTLDS)**: Test Mn-targeting drugs against persistent symptoms, as they may target viable spirochetes that survive standard therapy
- **Pediatric Formulations**: Develop child-safe narrow-spectrum agents to avoid broad-spectrum antibiotic risks

5.2 Resistance Prevention

Built-in safeguards to minimize resistance evolution:

- **Multi-Target Inhibition**: Combine BmtA inhibition with another essential pathway (e.g., mevalonate + Mn transport)
- **Essential Target Selection**: Focus on BmtA as the sole manganese transporter makes it difficult for the pathogen to develop resistance through redundant pathways
- **Host-Targeting**: Develop drugs targeting host Mn-handling proteins (e.g., calprotectin mimetics) to make resistance evolution impossible

5.3 Safety and Narrow-Spectrum Validation

Essential for regulatory approval and microbiome preservation:

- **Selectivity Screens**: Test all candidates against gut commensal panels (*Bacteroides*, *Lactobacillus*, *Clostridioides*)
- **Iron-Sparing Mechanism**: Exploit *B. burgdorferi*'s iron-independent metabolism to avoid off-target effects on iron-dependent human enzymes or microbiota
- **Tick Microbiome Impact**: Assess environmental safety for reservoir-targeted therapies in wildlife [19]

6 Conclusion

Borrelia burgdorferi has evolved an iron-independent, manganese-centric metabolism where manganese is both armor and Achilles' heel. The metal is essential for antioxidant defense and virulence, yet its transport and homeostasis represent critical vulnerabilities that the host immune system naturally targets. Recent discoveries—including BmtA's druggability, the toxicity of manganese imbalance, and AI-accelerated structure prediction—provide multiple validated pathways for developing narrow-spectrum, resistance-resistant therapeutics. The combination of traditional metabolic modeling with AlphaFold-assisted design offers an unprecedented opportunity to transform Lyme disease treatment within the next decade.

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References

[1] Hacker News Community. Manganese is lyme disease's double-edge sword. Hacker News Discussion, November 2025. URL https://news.ycombinator.com/item?id=45928709. Verified: URL accessible, Hacker News discussion thread that inspired this expanded analysis.

[2] Amanda Morris Woodruff. Manganese is lyme disease's double-edge sword. Northwestern Now, November 2025. URL https://news.northwestern.edu/stories/2025/11/manganese-is-lyme-diseases-double-edge-sword. Verified: URL accessible, Northwestern University press release describing Hoffman and Daly's research on manganese vulnerabilities in Borrelia burgdorferi.

[3] Z. Ouyang, M. He, T. Oman, X. F. Yang, and M. V. Norgard. A manganese transporter, bb0219 (bmta), is required for virulence by the lyme disease spirochete, borrelia burgdorferi. *Proceedings of the National Academy of Sciences*, 106:3449–3454, 2009. doi: 10.1073/pnas.0812999106. URL https://doi.org/10.1073/pnas.0812999106. Verified: DOI accessible. Original reference incorrectly listed as 2018 J Bacteriol.

[4] C. A. Whitehouse, L. R. Williams, and F. E. Austin. Identification of superoxide dismutase activity in borrelia burgdorferi. *Infection and Immunity*, 65(11):4865–4868, 1997. Verified via search. Original reference incorrectly listed Posey and Gherardini. Requires DOI.

[5] P. Wang et al. Metalloproteomic analysis of borrelia burgdorferi. *PLoS Pathogens*, 15:e1007873, 2019. Requires verification of full author list and DOI.

[6] P. J. Gwynne, C. A. Broberg, M. C. Miller, W. J. Chazin, E. P. Skaar, D. P. Giedroc, and J. T. Skare. Metal homeostasis in borrelia burgdorferi: a unique manganese-dependent pathogen. *Trends in Microbiology*, 28:770–783, 2020. Requires DOI verification.

[7] D. P. Giedroc and T. E. Kehl-Fie. The intersection of bacterial metal homeostasis and infectious disease. *Nature Reviews Microbiology*, 19:77–90, 2021. Requires DOI verification.

[8] T. E. Kehl-Fie, S. Chitayat, M. I. Hood, S. Damo, N. Restrepo, C. Garcia, K. A. Munro, W. J. Chazin, and E. P. Skaar. Nutrient metal sequestration by calprotectin inhibits bacterial superoxide defense, enhancing neutrophil killing of staphylococcus aureus. *Cell Host & Microbe*, 10:158–164, 2011. Verified via search. Original reference incorrectly listed as 2015, vol 18. Requires DOI.

[9] Centers for Disease Control and Prevention. Treatment and intervention for lyme disease, 2024. URL https://www.cdc.gov/lyme/treatment/index.html. Verified: URL accessible, official CDC guidance.

[10] Mayo Clinic. Lyme disease: Diagnosis and treatment, 2025. URL https://www.mayoclinic.org/diseases-conditions/lyme-disease/diagnosis-treatment/. REQUIRES URL VERIFICATION - Previous URL pointed to SARS page.

[11] R. B. Nadelman, J. Nowakowski, D. Fish, R. C. Falco, K. Freeman, D. McKenna, P. Welch, R. Marcus, M. E. Agero-Rosenfeld, D. T. Dennis, and G. P. Wormser. Prophylaxis with single-dose doxycycline for the prevention of lyme disease after ixodes scapularis tick bite. *New England Journal of Medicine*, 345:79–84, 2001. Corrected year from 2003 to 2001. Requires DOI.

[12] J. J. Halperin et al. European guidelines on diagnosis and treatment of lyme neuroborreliosis. *The Lancet Neurology*, 18:999–1009, 2019. Requires verification of full author list and DOI.

[13] J. D. Forrester and P. Mead. Lyme carditis: diagnosis and management. *Circulation*, 138:e62–e64, 2018. Requires DOI verification.

[14] A. C. Steere and S. M. Angelis. Therapy for lyme arthritis: strategies for the treatment of antibiotic-refractory arthritis. *Arthritis & Rheumatism*, 54(10):3079–3086, 2006. doi: 10.1002/art.22131. URL https://doi.org/10.1002/art.22131. Verified: DOI accessible. Original reference incorrectly listed as 2007.

[15] J. A. Branda and A. C. Steere. Laboratory diagnosis of lyme borreliosis. *Clinical Microbiology Reviews*, 34(2):e00018–19, 2021. doi: 10.1128/CMR.00018-19. URL https://doi.org/10.1128/CMR.00018-19. Verified: DOI accessible. Original reference listed Adrion as author - cannot verify.

[16] S. Warshafsky, D. H. Lee, L. K. Francois, J. Nowakowski, R. B. Nadelman, and G. P. Wormser. The efficacy of single-dose prophylaxis with azithromycin for the prevention of lyme disease after ixodes scapularis tick bite. *Clinical Infectious Diseases*, 43:651–658, 2006. Requires DOI verification.

[17] A. Berende, H. J. M. ter Hofstede, F. J. Vos, H. van Middendorp, M. L. Vogelaar, M. Tromp, F. H. J. van den Hoogen, A. R. T. Donders, A. W. M. Evers, and B. J. Kullberg. Randomized trial of longer-term therapy for symptoms attributed to lyme disease. *New England Journal of Medicine*, 374:1209–1220, 2016. Requires DOI verification.

[18] D. Wagh, V. R. Pothineni, M. Inayathullah, S. Liu, K. M. Kim, and J. Rajadas. Borreliacidal activity of borrelia metal transporter a (bmta) binding small molecules by manganese transport inhibition. *Drug Design, Development and Therapy*, 9:805–816, 2015. doi: 10.2147/DDDT.S76063. URL https://doi.org/10.2147/DDDT.S76063. Verified: DOI accessible. Original reference incorrectly listed as Li 2021 in Ticks Tick-borne Dis.

[19] S. Magnúsdóttir et al. A genome-scale metabolic model of borrelia burgdorferi predicts species-specific vulnerabilities. *PLoS Computational Biology*, 17:e1009204, 2021. Requires verification of full author list and DOI.

[20] K. Brangulis, I. Petrovskis, A. Kazaks, K. Tars, and R. Ranka. Structure of the borrelia burgdorferi atp-dependent protease ftsh. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics*, 1871:140843, 2023. Requires DOI verification.

[21] F. Wong, A. Krishnan, and J. J. Collins. Analyzing the potential and limitations of alphafold in drug discovery. *Molecular Systems Biology*, 18:e11081, 2022. URL

https://news.mit.edu/2022/alphafold-potential-protein-drug-0906. Verified: URL accessible, MIT News coverage of Molecular Systems Biology publication.

[22] M. Jaderberg, A. Stecula, and P. Savy. Rational drug design with alphafold 3. Isomorphic Labs Blog, August 2024. URL https://www.isomorphiclabs.com/articles/rational-drug-design-with-alphafold-3. Verified: URL accessible, official Isomorphic Labs article.

[23] National Institutes of Health. Review of alphafold 3: transformative advances in drug discovery. PubMed Central, 2024. Template reference - PMC number needs verification.