Anti-Inflammatory and Immunomodulatory Effects of Macrolides: Biological Mechanisms and Clinical Use in the Management of Chronic Diseases

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Background and Objectives: Macrolides are well established antimicrobial agents; however, accumulating evidence suggests they also possess clinically meaningful anti-inflammatory and immunomodulatory properties. This review aimed to evaluate the biologic mechanisms underlying these effects and assess the clinical evidence supporting the use of macrolides as adjunctive therapy in the management of chronic diseases. Additionally, safety considerations and the potential impact of long-term macrolide therapy on antimicrobial resistance were examined.

Methods: A structured literature review was conducted using the PubMed electronic database. Search strategy development was guided by a PICO framework and included English-language studies published between 1987 and 2023. Adults (≥18 years) with chronic diseases treated with macrolide therapy were included, with randomized controlled trials prioritized. Chronic disease states reviewed included chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), asthma, chronic rhinosinusitis (CRS), non-cystic fibrosis bronchiectasis (NCFB), diffuse pan bronchiolitis, and rheumatoid arthritis (RA). Data were organized using a literature matrix and synthesized through thematic analysis focusing on clinical efficacy, mechanisms of action, dosing strategies, symptom effects, adverse events, and antimicrobial resistance.

Results: Macrolides demonstrated multiple immunomodulatory mechanisms, including promotion of anti-inflammatory macrophage polarization, modulation of T-cell responses, suppression of pro-inflammatory cytokines and chemokines, inhibition of NF-κB signalling, and disruption of bacterial biofilm formation and quorum sensing. The strongest clinical evidence was observed in COPD, CF, and NCFB, where long-term macrolide therapy consistently reduced exacerbation frequency, improved quality of life, and, in several studies, stabilized lung function. More limited and heterogeneous evidence was identified in asthma, CRS, and RA, where benefits appeared restricted to selected patient populations, including atypical bacterial infection, low-IgE CRS, post-operative CRS, and early active RA. Across all disease states, long-term therapy was consistently associated with increased antimicrobial resistance, while ototoxicity, gastrointestinal intolerance, and potential QT prolongation remained important safety considerations.

Discussion: The available evidence suggests that the clinical benefits of macrolides extend beyond antimicrobial activity and are likely mediated through multiple complementary anti-inflammatory, immunomodulatory, and anti-virulence mechanisms. Their therapeutic value appears greatest in chronic respiratory diseases characterized by recurrent exacerbations and persistent neutrophilic inflammation. Conversely, evidence supporting routine use in asthma, CRS, and rheumatologic disease remains insufficient. Careful patient selection and ongoing monitoring are essential to balance clinical benefit against adverse effects and antimicrobial stewardship concerns.

Conclusions: Macrolides represent promising disease-modifying adjunctive therapies for selected chronic inflammatory diseases, particularly COPD, CF, and NCFB. Future research should prioritize biomarker-guided patient selection, optimization of dosing strategies, and investigation of long-term effects on antimicrobial resistance and the airway microbiome to better define their role in chronic disease management.

Keywords: macrolides; immunomodulation; COPD; asthma; rhinosinusitis; cystic fibrosis

Estimating the Carbon-Footprint, Cost, and Healthcare Resource Use in the Last Week of Life for Patients who Died on Inpatient Wards: A Retrospective Cohort Study

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Background and Objectives: The clinical teaching unit (CTU) is a universal educational model for medical trainees in the setting of acute ward-based care. The presumption of the standard of care on a CTU is to cure acute illness, which may not reflect the patient's prognosis, goals of care or values. It is unknown how the CTU model affects care for inpatients with terminal illness with or without palliative care goals. We hypothesize that there may be under-recognition of end-of-life (EOL) presentations on the CTU and the value of shifting towards care plans that demedicalize death. To examine the timing of recognition of likely death and subsequent transition to comfort-focused goals of care (GoC); to quantify medicalization of expected death; and lastly, to quantify resource use and their associated carbon emission equivalents pre- and post-transition.

Methods: We conducted a retrospective cohort study of adult inpatients who died during admission to the 8.2 CTU at the Halifax Infirmary between January 1, 2023, and December 31, 2023 (N=103). Patients who died in other hospital settings were excluded. Electronic medical chart reviews were performed to collect demographic data and resource utilization data for the final 7 days of life. Resource data informed analyses of inappropriate medicalization, cost, and associated carbon emissions. The primary outcomes were i) the proportion of medicalized days; ii) total inpatient costs; and iii) total estimated healthcare-associated greenhouse gas emissions during the final week of life. Multivariable logistic regression was used to describe predictors of medicalized death. Total inpatient costs and carbon emissions were quantified via generalized linear models with gamma distribution and log link.

Results: In our study population, 86.7% of patients experienced a medicalized death. From the time of recognition of imminent death, patients experienced a median of 2 medicalized days (IQR 1-4) and a median proportion of 66.7% medicalized days (IQR 25-100%) before they died. A delay of ≥ 2 days to transition a patient to comfort care after imminent death was recognized

increased the proportion of medicalized days by 43.8% (95% CI 32.02–55.65; $p < 0.001$). The mean total inpatient cost in the final week of life was $8,078 (SD $1,991); costs were not explained by length of stay (6.8 vs 6.6 days for top 10% of patients and remaining 90%, respectively). For carbon costs, the median total emissions in the final week of life was 140.5 $kgCO_2e$ (IQR 64.66-277.03), with medications contributing to 77% of total emissions. Each additional day of delay to transition to comfort care was associated with a 4% increase in total inpatient costs (CR 1.04, 95% CI 1.01–1.07, $p = 0.009$) and a 21% increase in carbon emissions (ER 1.21, 95% CI 1.09–1.35, $p = 0.001$).

Discussion: On the CTU, most acutely ill inpatients experienced a medicalized death. After a clinician recognized imminent death, a delay to transition to comfort care increased medicalizing interventions, resource utilization, and carbon emissions.

Conclusions: The reasons for delay are likely multifactorial; thus, changes in institutional policy, additional training and excellent communication between teams and inpatient-family units may allow for a comfortable, de-medicalized death. Decreasing inappropriate interventions and providing goal-focused care is within the scope of the CTU model, and empowers teams to be resource stewards and provide decarbonized care.

Keywords: Medicalized death; greenhouse gas emissions; clinical teaching unit (CTU)

Unheard Voices: A Narrative Review to Inform Integration of Lived Experience of Homelessness and Substance Use into Research and Service Design

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Background and Objectives: Homelessness and substance use disorders are complex public health issues that are influenced by social, economic, and structural factors. Despite increasing recognition of the importance of lived experience in health research and service development, individuals affected by homelessness and substance use remain underrepresented in research, policy, and program design. This narrative review examined existing literature on homelessness, substance use disorders, and participatory frameworks to better understand the conditions that shape these experiences and identify how lived experience can be meaningfully integrated into research and service design. This review aimed to 1) understand factors associated with homelessness, substance use disorders, and service use, 2) identify barriers to participation in research and service design, and 3) explore how lived experience can be more effectively incorporated into research and service design.

Methods: A narrative review of peer-reviewed and grey literature was conducted using PubMed, Google Scholar, and targeted Google searches to identify government reports, policy documents, and organizational publications. Search terms included combinations of homelessness, substance use disorders, lived experience, participatory research, service design. Searches began broadly using terms related to homelessness and substance use disorders, then were refined to focus on participation in research and service design among these populations. Approximately 200 sources were screened for relevance, with titles and abstracts reviewed first, followed by full-text review of sources meeting initial criteria. Sources were included if they addressed homelessness, substance use disorders, lived experience, participatory research, or service design. Of approximately 200 sources screened, 93 met inclusion criteria and were included in the narrative synthesis, including 59 peer-reviewed publications, 26 government and organizational reports, and 8 books or foundational texts. Eligible sources examined social determinants of health, risk and protective factors, service access, and participatory approaches involving marginalized populations, including Indigenous peoples and 2SLGBTQIA+ youth. Patient and public involvement (PPI), co-design, and the IAP2 Spectrum of Public Participation emerged as recurring participatory frameworks during the review rather than being predefined. Findings were synthesized using thematic analysis.

Results: Poverty, trauma, discrimination, and limited access to culturally safe care were identified as key contributors to homelessness and substance use disorders. Stigma and restrictive service requirements were identified as common barriers to accessing services. Barriers to meaningful participation included tokenism, inadequate compensation, risks of re-traumatization, and institutional structures that limit decision-making capacity among people with lived experience. Participatory frameworks, including PPI, co-design, and the IAP2 Spectrum, provided varying approaches to structuring engagement, emphasizing the importance of shared decision-making rather than consultation alone. Examples of co-designed and peer-led initiatives demonstrated that when individuals with lived experience are included as collaborators and decision-makers rather than solely as participants, services may become more responsive, trusted, and effective.

Discussion: The findings suggest that incorporating lived experience into research and service design can improve the relevance and effectiveness of research and services. However, participation is often limited by existing power imbalances and structural barriers. Frameworks such as PPI and co-design offer guidance for engagement, but their effectiveness depends on how participation is implemented in practice. Trauma-informed approaches, equitable compensation, peer leadership, and long-term institutional commitment are needed to translate these frameworks into meaningful participation.

Conclusions: This review identifies a persistent gap between institutional knowledge and the lived realities of individuals affected by homelessness and substance use disorders. Addressing this gap requires shifting decision-making power toward those most affected by research and service decisions. Centering lived experience is not only a strategy for improving outcomes but also a commitment to health equity, human rights, and social justice. Future research and service design should prioritize qualitative and participatory approaches that elevate underrepresented voices and generate community-informed evidence to guide responsive policy and service design.

Keywords: homelessness; substance use disorders; lived experience; participatory research; service design