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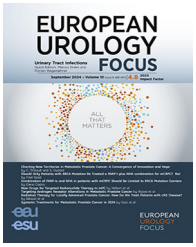

Mini Review

Glycomimetics as Candidates for Treatment and Prevention of Catheter-associated Biofilms Formed by Pseudomonas aeruginosa

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Abstract

Bacteria develop biofilms for protection and persistent colonization. Biofilms of pathogenic bacteria can lead to serious medical problems. Bacterial biofilms on catheters used in the treatment of urinary tract diseases represent a major challenge for antibiotic therapy. Several attempts to eradicate biofilms using classical antibiotics and various alternatives, including antibiotic treatment of surfaces, surfaces that release silver ions, and surfaces with anti-adhesive properties, have not shown clinical efficacy in biofilm prevention or removal. *Pseudomonas aeruginosa* is one of the most problematic biofilm-forming uropathogens and accounts for approximately 10% of urinary tract infections. Novel glycomimetics that inhibit bacterial lectins have shown promising results in the prevention of *P. aeruginosa* biofilms and in interference with bacterial virulence. This mini-review summarizes the status of glycomimetic development and provides a perspective on their use in clinical practice.

Patient summary: For patients with recurrent urinary tract infections and patients needing long-term catheter use to manage urinary problems, biofilms formed by bacteria can be a problem and are difficult to treat. New compounds that mimic carbohydrates, called glycomimetics, have shown promise in inhibiting these bacteria and the biofilms they form. More research on these compounds is needed before they can be used to treat patients.

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1. Introduction

Difficult-to-treat chronic infections are mainly the result of biofilm formation by different species of pathogenic bacteria. Urinary catheters are regularly associated with biofilm infections. It is estimated that urinary catheters account for more than 60% of health care–associated urinary tract infections (UTIs) [1].

Biofilms are a protective shield for the pathogen and thwart the action of both the host's immune defense and

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antibacterial agents intended to eradicate the pathogen. Polymeric biofilm components such as extracellular DNA and polysaccharides create a microenvironment that allows locally distinct concentrations, leading to the development of resistance and further increasing antimicrobial resistance in UTIs [2]. Here we focus on persistent biofilms produced by the Gram-negative bacterium *Pseudomonas aeruginosa,* which accounts for approximately 10% of UTIs [3].

2. Pathophysiology

Biofilm formation is a complex process triggered by the physical nature of the colonized surface and quorum sensing of individual bacterial cells and receptor molecules on biological surfaces. *P. aeruginosa* colonization involves binding to carbohydrate epitopes of the host through bacterial lectins, which serve as adhesins. *P. aeruginosa* LecA binds to galactoside conjugates and LecB binds to fucoside and mannoside conjugates. Both lectins are also crucial for biofilm formation on abiotic surfaces devoid of carbohydrate receptors via cross-linking with exopolysaccharides. In addition, LecA causes disintegration of host cells membranes and LecB impairs cell migration (eg, immune cell passage across endothelial monolayers) and consequently the immune response and wound healing in the host [4].

3. Previous strategies to mitigate biofilms

Several strategies for biofilm mitigation have been investigated, including antibiotic treatment of surfaces, surfaces that release silver ions, and surfaces with anti-adhesive properties [5]. None of the current biofilm prevention strategies was clinically successful with respect to the most relevant endpoint of catheter-associated UTI [1]. Given these drawbacks, research has also focused on quorum sensing inhibitors and plant agents such as essential oils [6] and polyphenols, including curcumin and resveratrol. However, polyphenols showed unspecific reactions and ambiguous results [7].

4. Novel strategies involving glycomimetics

Various uropathogens use glycosides on the cell surface as receptors to colonize their hosts. Therefore, glycomimetics with activity against biofilm-forming *Escherichia coli* strains are in clinical development [8]. Because of the particular complexity of *P. aeruginosa* biofilms [5], the use of glycomimetics targeting *P. aeruginosa* lectins is a sensible strategy for containment. Novel glycomimetics such as C-glycoside derivatives of the natural LecB ligands inhibited biofilm formation by *P. aeruginosa* in vitro [9]. First in vivo tests of the frontrunner glycomimetic LecB inhibitor revealed inhibition of its detrimental effects on the immune response in mice [4]. Importantly, the C-glycoside glycomimetic class of compounds has shown favorable pharmacokinetics in mice, with high concentrations >1 mM in urine after a single oral dose of 10 mg/kg [9].

Follow-up compounds with a tenfold increase in potency for LecB have been identified [10]. In addition, highly potent LecA inhibitors with beneficial effects on LecA-mediated virulence have been described [10]. High urine concentrations after intravenous dosing in mice and rats suggest their further clinical evaluation against UTIs caused by *P. aeruginosa*. Thus, lectin inhibitors appear a promising option to prevent *P. aeruginosa* UTI biofilm formation or treat established biofilms in conjunction with a standard of care antibiotic.

5. Conclusions

Given the importance of controlling bacterial biofilms in UTIs, further studies with innovative agents are essential. Potentiated by the increasing spread of antimicrobial resistance among bacterial pathogens, these infections pose a fundamental medical problem in the "post-antibiotic" era [5].

Glycomimetic lectin antagonists have shown promising results against the virulence of and biofilm formation by *P. aeruginosa*, one of the most important pathogens producing biofilms, as highlighted in the 2024 list of priority bacterial pathogens published by the World Health Organization. High renal excretion of these compounds results in high urinary concentrations, which suggests that further assessment in *P. aeruginosa* models of UTI is warranted.

Conflicts of interest: The authors have nothing to disclose.

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