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Inhaled anti-infective chemotherapy for respiratory tract infections: Successes, challenges and the road ahead☆

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ABSTRACT

One of the most common causes of illnesses in humans is from respiratory tract infections caused by bacterial, viral or fungal pathogens. Inhaled anti-infective drugs are crucial for the prophylaxis and treatment of respiratory tract infections. The benefit of anti-infective drug delivery via inhalation is that it affords delivery of sufficient therapeutic dosages directly to the primary site of infection, while minimizing the risks of systemic toxicity or avoiding potential suboptimal pharmacokinetics/pharmacodynamics associated with systemic drug exposure. This review provides an up-to-date treatise of approved and novel developmental inhaled anti-infective agents, with particular attention to effective strategies for their use, pulmonary pharmacokinetic properties and safety.

Contents

Abbreviations: CMS, Colistimethate sodium; CF, cystic fibrosis; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; IFN, interferon; MRSA, methicillin-resistant *Staphylococcus aureus*; RSV, respiratory syncytial virus.

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1. Introduction

One of the most common causes of illness in the human population by far arises from respiratory tract infections [1]. Ventilator-associated pneumonia is the most frequent nosocomial infection in intensive care units. Due to millions of physician visits, hospitalizations and lost work hours, the economic cost of respiratory infections runs into hundreds of billions each year [1–3]. For influenza epidemics alone in the USA, the total annual economic burden using projected statistical life values is approximately $87.1 billion [4]. Important human pathogenic organisms responsible for respiratory infections include bacteria (e.g. *Pseudomonas aeruginosa*), fungi (e.g. *Aspergillus* spp.), and viruses (e.g. respiratory syncytial virus, and influenza virus), all of which have a high cumulative burden of morbidity and economic losses [5]. Inhaled anti-infective drugs play a pivotal role in the prophylaxis and treatment of these common respiratory infections. The most effective treatment involves aerosolized drug administration that delivers the anti-infective agent directly to the respiratory tract, thereby achieving drug concentrations sufficient to eradicate the pathogenic organisms at the site of infection. Importantly, aerosolized administration greatly reduces potential toxicity associated with systemic exposure. The primary mode for aerosolized pulmonary delivery of anti-infective agents is via nebulization, using jet systems, ultrasonic systems, and other systems that use a vibrating mesh/aperture plate [6].

Although aerosol delivery has many advantages, there is a paucity of data on the safety, efficacy and pulmonary pharmacokinetics of anti-infectives administered via this route. Moreover, very few drugs are specifically designed and formulated for pulmonary delivery or under development. Future advances will depend upon development of novel delivery devices [7] and formulations [8], optimization of pulmonary pharmacokinetics/pharmacodynamics (PK/PD) of the drug, and broad-spectrum inhaled agents. Importantly, potent inhaled

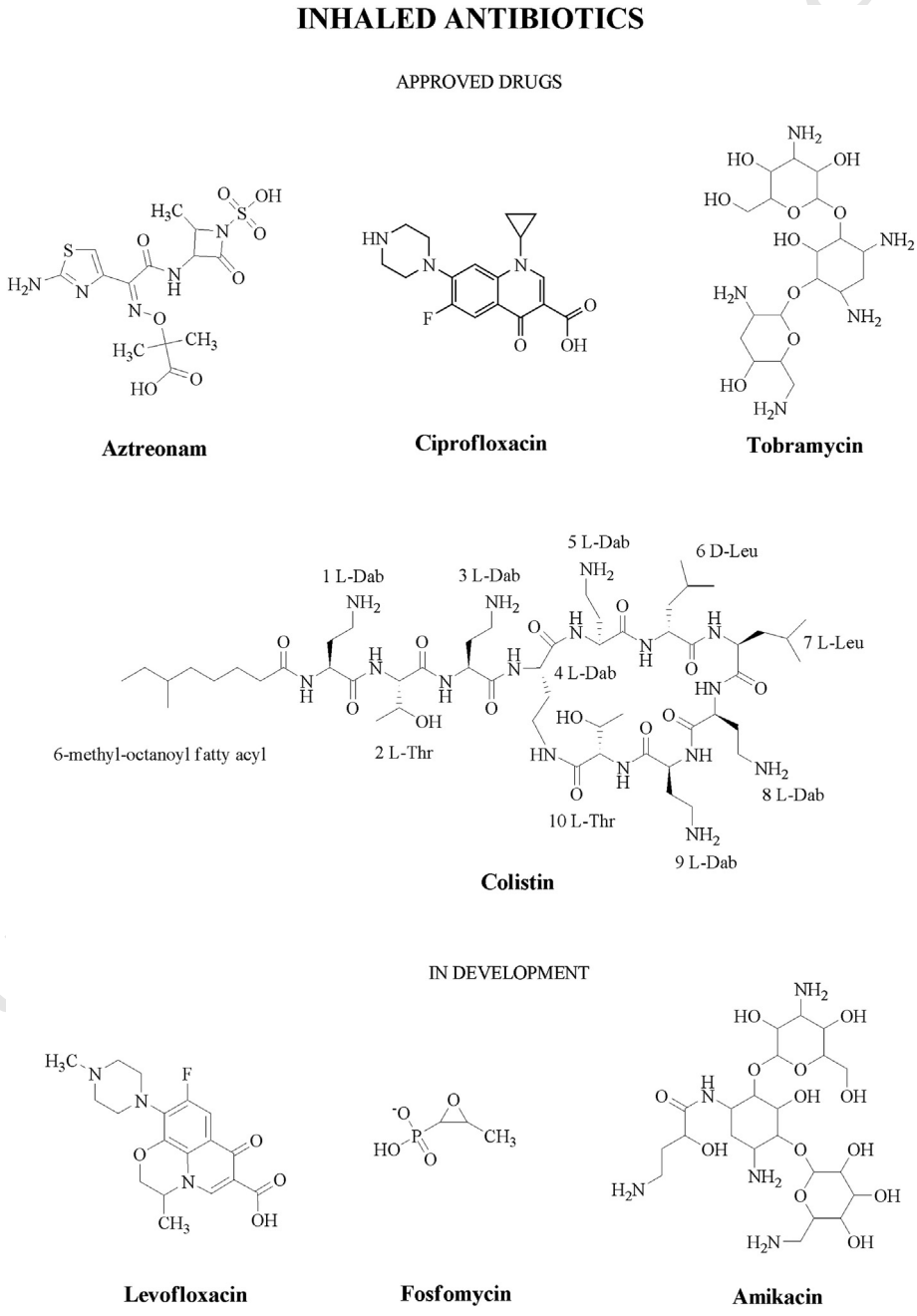

Fig. 1. Chemical structures of inhaled antibiotics.

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