International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 14, Issue 2, 2022

Review Article

# INTRANASAL DELIVERY IN MANAGING ANTIBIOTIC RESISTANCE IN 'BRAIN INFECTIONS'

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*Received: 08 Nov 2021, Revised and Accepted: 12 Jan 2022*

**ABSTRACTs**

According to World Health Organization, WHO, antibiotic resistance is one of the biggest threats to global health, food security and development today. The means of delivering antibiotics to treat several brain infections, especially meningitis and encephalitis, have been inherently difficult, due to the presence of highly protective physiological barriers, mainly the blood-brain barrier (BBB), cerebrospinal fluid (CSF) that impairs the efficacy and bioavailability of antibiotics from reaching the susceptive organism. Many attempts have been made to optimize the therapeutic prognosis of such infections through the parenteral and intrathecal route of administration. These alternative routes have incited inadequate efficacy along with associated adverse effects. However, scientists have now considered the intranasal route (non-invasive) as a breakthrough to such inherent challenges. Moreover, several *in vivo* and *ex vivo* studies suggested evidence of the effectiveness of nose-to-brain delivery in treating bacterial and viral infections, thereby limiting the chance of antibiotic resistance. Targeting the multidrug resistance gram-positive and negative bacterias, a study was reported using nanoemulsion of *Syzygiumaromaticum* and *Thymus vulgaris* essential oils via the intranasal route. The result indicated the maximum inhibition of multi-drug resistance bacterias upon intranasal administration. Therefore, this study focuses to highlight the potential of intranasal delivery in the optimization of CNS infections and the prevention of antibiotic resistance.

**Keywords**: Antibiotic-resistance, Brain infection, Physiological barriers, Nose-to-brain delivery, Intranasal delivery


DOI: https://dx.doi.org/10.22159/ijcpr.2022v14i2.1559 Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

## INTRODUCTION

Infections caused by various species of bacteria, viruses, fungus, and other parasitescan be terminal infections if they happen to affect Central Nervous Systems (CNS). Meningitis is one such infections and refers to the inflammation of "membranes that surround the brain and spinal cord" (meninges); the inflammation can be caused by infections, adverse effects of certain drugs or autoimmune disease [1]. Meningitis instigated by bacteria is termed as bacterial meningitis, and it is rare and the most fatal type [2]. Other types include Pneumococcal, Meningococcal, Haemophilus influenza, Viral, and non-infectious meningitis that is caused by autoimmune disorders and adverse effect of certain medication**,** among others. Moreover, most fetal bacterial meningitis is caused by Listeria and *E. coli* species [3, 4]. Besides, encephalitis (inflammation of the brain) is commonly caused by herpes simplex types 1 and 2 viruses, as well as arboviruses, that often transmit from mosquito and other biting insects. However, encephalitis cases are rarely diagnosed among infected persons; about 60% of the case remain undetected. The prevalence rate of 2:1,000,000 per year in USA [1]. Understanding the pathophysiology CNS related infections is very essential for imporoving their clinical prognosis, most importantly, through overcoming their inherent resistance to antibiotic.

Besides, the World Health Organization reported the progressive increment in antibiotic misuse and subsequent resistance that result in a high mortality rate to about 700,000-per year worldwide in addition to the economic burden it causes [2, 5]. However, the irrational use of conventional antibiotics is the most contributing factor to antibiotic resistance [6]. Moreover, targeting brain infections with antibiotics remains inherently challenging [7], because many of these conventional antibiotics show extremely low oral bioavailability, frequent administration, patient noncompliance, cost of medication, and poor prognosis [8]. Besides, CNS-related infections attributes to high morbidity and mortality rate even in developed countries like England, USA, Russia, and France. However, the Blood-brain barrier BBB is a highly protective barrier that serves as the rate-limiting strep for the drugs, including antibiotics to reach optimal bioavailability and target the specific site of action in the brain [9]. M. Fung, *et al.*, reported that BBB limited the permeation of approximately 98% of drugs from reaching their desired site of actions [10]. Therefore, scientists have studied many techniques to maximize the bioavailability of such drugs by bypassing the hindrance of BBB [11]. Amongst, Invasive (carrier-mediated) delivery was suggested earlier to as an option for targeting brain infections, but its clinical applications are limited by lack of safety, cost and many inconveniences; alternatively, noninvasive (intranasal) administration of the drugs is now the best techniques to bypass BBB and target brain infections and other related disorders. Nevertheless, Many *in vivo* and ex vivo studies have also shown that nose-to-brain delivery is effective in the treatment of bacterial and viral infections and has reduced antibiotic resistance. Therefore, this research is focused on the potential of intranasal delivery optimization for CNS infection subsequent prevention of antibiotic resistance.

### Concept of antibiotic resistance

Antibiotic resistance occurs as germs such as bacteria and fungi can kill the medicines meant for their destruction. It means the germs are not destroyed and are still rising. Antibiotic-resistant germ-caused infections are difficult to treat and sometimes impossible. In most cases, infections resistant to antibiotics need prolonged hospital stays, extra medical visits, and expensive and harmful alternatives. Antibiotic resistance does not mean the body becomes antibiotic-resistant; it is because the bacteria become antibiotic-resistant. Antibiotic resistance can affect individuals and the medical, veterinary, and agricultural industries at any point in life and is one of the worst public health issues on the planet. In the U. S., at least 2.8 million people are infected with antibiotic-resistant bacteria or fungi per year, resulting in more than 35,000 deaths [12]. Nobody can avoid the risk of resistive infections completely, but some people are at higher risk than others (e. g. people with chronic diseases). If antibiotics become less effective, we lose the ability to treat infection and control threats to public health [13, 14]. The ability to battle antibiotic infections, including joint replacements, Organ transplants, cancer treatments, and chronic disorders such as diabetes, asthma, and rheumatoid arthritis, are contingent upon several developments in medicines. The way it prescribes and uses antibiotics needs to change in the world urgently [15]. Despite the improvement in behavior, antibiotic resistance is still

a major problem even though new drug drugs are created. Changes in behavior will also include steps to reduce the spread of diseases through vaccination, washing of hands, healthier sex, and nutritious food [16].

Antibiotic tolerance and resistance have become global threats. New pathways for resistance are being developed and distributed globally, which challenge our ability to treat common infectious diseases [17, 18]. The growing number of infections, such as pneumonia, tuberculosis, blood poisoning, gonorrhea, and food diseases, are becoming more, more difficult, and often impossible to treat because antibiotics are less effective. Where antibiotic products may be obtained without a prescription for human or animal use, resistance grows and spreads further. Furthermore, antibiotics are frequently over-prescribed by and over-used by health workers and veterinarians in countries without formal care guidelines. Before immediate action, we are moving into a post-antibiotic age, where common infections and minor injuries will kill once again [19, 20].

**Mechanism of intranasal delivery of antibiotics to 'brain infections**

In general, the nose-to-brain delivery mechanism is not clearly understood [21]. The large surface area and high vascularization [22] and anatomical features of nasal epithelial tissues ease the permeation of molecules to CNS through different pathways [23]. Furthermore, the anatomy and physiology of the intranasal route provide insight on its possibility to be a breakthrough in brain delivery targeting. Thanks to the presence of olfactory and trigeminal pathways [24]. The olfactory region is the most essential means for nose-to-brain delivery of drugs; therefore, it was discovered to be the "portal for drug resistance" However, this complex process involves the interactions between the nasal mucosa, lymphatic plexus, perineural sheaths, in subarachnoid space [25, 26]. The drug delivery through the intranasal route is given by three main pathways, namely, intracellular diffusion, paracellular transportation, and receptor-mediated or trans/endo-cytosis, a schematic representation of the same is done in Fig. 1. High lipophilicity and low molecular weight of the drug is a major prerequisite for its absorption through these pathways [27, 28]. Besides, the trigeminal nerve is an important pathway that connected the olfactory, respiratory epithelium, and CNS in the pons. Moreover, its short terminal branch in the olfactory bulbs (chemosensory zone) is very important for brain targeting, because it is where the highest drug concentration observes in CNS [29-31]]. The Ekberg *et al.*, the study highlighted the mechanism of brain infection by *Burkholderiapseudomallei* bacteria via the pathway of the trigeminal nerve, and this proved the greater possibility of targeting brain infections with antibiotic drugs via the same route [32]. Nanosized and small molecules are many upper advantages to pass BBB limitation through carrier-mediated transportation, the molecule of molecular weight of<400 Da and hydrogen bonds<8, possessed high preference of free diffusing through lipid-mediated carriers across BBB to the brain [33, 34]. Therefore, employing the concept of nanotechnology will also be essential for drug absorption in all drug delivery systems including nose-to-brain. More so, these concepts have been understudying by the scientist and several clinical trials are on-going while some antibiotics for intranasal delivery to CNS have been approved.

***In vitro* studies**

F. Ronald *et al.*, targeted the multidrug resistance gram-positive and negative bacterias with nanoemulsion of Syzygiumaromaticum and Thymus vulgaris essential oils using the intranasal route. The result indicated the maximum inhibition of multi-drug resistance bacteria upon intranasal administration [35]. P. Manda *et al.*, delivered cefotaxime to treat brain infection through the intranasal route and the Pharmacokinetic investigation shows high bioavailability of the cefotaxime in the brain by administration intranasally [36]. Nano-aerosol of AmB has shown higher bioavailability than oral, parenteral, and intrathecal [37, 38]. S. T. Lim *et al.* demonstrated a comparative *in vitro* study between intravenous and intranasal administration of Gentamicin antibiotics. The study result indicated the intranasally administered Gentamicin attained high bioavailability as compared to the intravenous route [39].

***In vivo* studies**

Petra J. *et al.*, induced meningitis using Streptococcus pneumonia on a murine model and demonstrated the efficiency of intranasal administration as a gold standard for the treatment of brain infection in humans [40].

Sakane *et al.* evaluated the bioavailability of cephalexin antibiotic using *in vitro* experiment on a rat model, and the study revealed the drug to have reach maximum safety concentration within 30 min, even though cephalexin was known to have poor bioavailability to CSF due to itslimited permeation to BBB when administered via other routes. The study concluded that the

bioavailabilityof cephalexin upon nasal administration is 166-fold higher than that of other routes [41]. D. Inoue *et al.* reported the administration of norfloxacin via the intranasal route increases its absorption rate. However, the study found the change in mucociliary clearance to have affected the bioavailability of norfloxacin after *in vivo* demonstration on Male Wistar rats. Therefore, the nose-to-brain delivery system can be the route of choice for delivering antibiotics like norfloxacin for targeting brain infections [44]. Joana S. *et al.* evaluated and compared the efficacy of levofloxacin upon intravenous and intranasal administration to healthy adult male.

Wistar rats. The *in vivo* pharmacokinetic examination reveals that intranasally, the levofloxacin attained a high concentration at a lower dose of 0.24 mg/kg while the intravenous route that shows the same concentration at the higher dose [42].

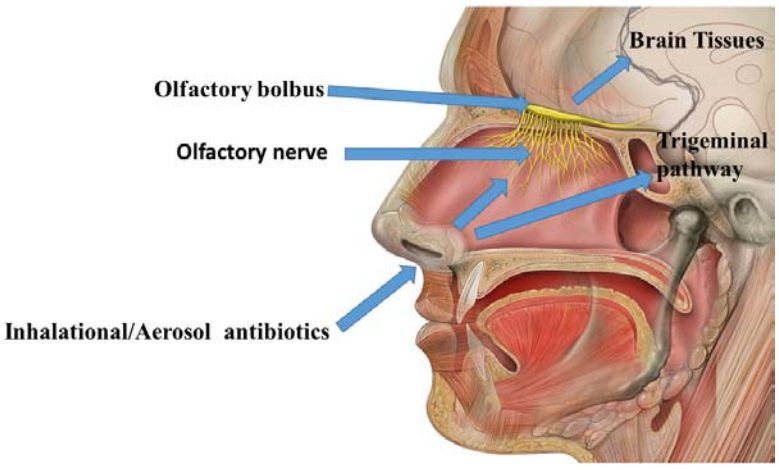


**Fig. 1: Mechanism of intranasal delivery of antibiotics to 'brain infections'**

**Challenges and future perspectives**

Bacterial infections are causing serious concern around the globe [43]. Owing to the global emergence of multidrug-resistant (MDR) bacterial pathogens, the efficacy of traditional antibiotics is decreasing. This cycle appears to be mainly triggered by indiscriminate and excessive use of antibiotics in non-infected patients and the food industry. New types of antibiotics with specific behavior against MDR pathogens need to be established urgently [44, 45]. Besides, due to the existence of highly protective physiological barriers, primarily BBB, CSF, which inhibited the effectiveness and bioavailability of antibiotics from reaching susceptible species, the means for delivery of antibiotics to treat many brain infections, particularly meningitis and encephalitis, have been difficult. There have been several efforts to improve the therapeutic prognosis of these infections, and insufficiency along the associated adverse effects is seen via a parenteral and intrathecal route of administration [46]. However, the clinical benefits of intranasal delivery were limited because of the effect of mucociliary clearance, enzymatic degradation of proteins, and peptides these limitations need to be addressed to optimize the clinical efficiency of intranasal delivery [47, 48]. Therefore, advanced research in this field is highly recommended.

## CONCLUSION

The menace of antibiotic resistance could be overcome through formulating intranasal antibiotics since the route is capable of bypassing the hindrance effect of the main physiological blood-brain barrier. However, brain infections can optimally be targeted, therefore, the clinical prognosis of deleterious CNS infections like meningitis, encephalopathy could effectively be improved.

## LIST OF ABBREVIATIONS

MDR: Multidrug-resistant, BBB: Blood brain barrier, BTB: Blood tumour barrier, CSF: Cerebrospinal fluid, CNS: Central Nervous System

## ACKNOWLEDGEMENT

The authors would like to acknowledge the contribution of their co-authors

## FUNDING

This work did not receive any funding in cash or kind

## CONFLICT INTERESTS

Declared none

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