ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Intranasal drug delivery devices are a potential contamination source of airways

Dispositivos intranasais de medicamentos são uma potencial fonte de contaminação das vias aéreas

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ABSTRACT

Background: The use of intranasal drug delivery devices (IDDD) for the treatment of allergic rhinitis (AR) is frequent because they are simple, efficient, and safe, and mainly because they are perceived as low-risk. However, it is speculated that contact between the nasal mucosa and an IDDD may give rise to infections once the nose is colonized by bacteria, and there are currently no proper instructions for IDDD sanitization. The objective of this study was to evaluate the possibility of contamination of an IDDD for topical medication after simulating use in healthy individuals. **Methods:** The in vitro study consisted of 14 healthy individuals of both sexes, between the ages of 18 and 24 years. Samples were collected immediately after the opening of each IDDD and after simulating use by the subjects. Afterwards, the samples were deposited in tubes and kept in an incubator at 37 °C. After 48 hours, the samples were inoculated on Müller-Hinton agar. Qualitative analyses of the appearance of the samples were performed after 24 and 48 hours, and after 72 hours the presence or absence of bacteria was evaluated macroscopically. **Results:** After 24 hours of incubation, 21.4% (n = 3) of the samples presented with a turbid appearance and after 48h, 71% (n = 10) of the samples presented with a turbid appearance and positive bacterial growth. **Conclusion:** The results suggest that IDDDs for topical medications may be important sources of contamination or recontamination of the nasal mucosa of individuals who are being treated for upper respiratory tract conditions. A better understanding of the risks of re-using IDDDs after previous contact with the nasal mucosa will improve guidelines on hygiene procedures and prevention of related risks.

Keywords: Administration, intranasal, nasal mucosa, contamination, bacteria.

RESUMO

Introdução: O uso de dispositivos intranasais para administração de medicamentos (IDDD) no tratamento da rinite alérgica (AR) é frequente, por serem simples, eficientes e seguros, e principalmente por serem de baixo risco. No entanto, especula-se que o contato entre a mucosa nasal e um IDDD possa causar infecções, uma vez que o nariz é colonizado por bactérias, e atualmente não há instruções adequadas para a higienização do IDDD. O objetivo deste estudo foi avaliar a possibilidade de contaminação de um IDDD para medicação tópica após simulação de uso em indivíduos saudáveis. **Métodos:** O estudo *in vitro* foi composto por 14 indivíduos saudáveis, de ambos os sexos, com idades entre 18 e 24 anos. As amostras foram coletadas imediatamente após a abertura de cada IDDD, e após a simulação do uso pelos sujeitos. Posteriormente, as amostras foram depositadas em tubos e mantidas em incubadora a 37 °C. Após 48 horas, as amostras foram inoculadas em ágar Müller-Hinton. As análises qualitativas da aparência das amostras foram realizadas após 24 e 48 horas, e após 72 horas a presença ou ausência de bactérias foi avaliada macroscopicamente. **Resultados:** Após 24 horas de incubação, 21,4% (n = 3) das amostras apresentaram aparência turva e, após 48h, 71% (n = 10) das amostras apresentaram aparência turva e crescimento bacteriano positivo. **Conclusão:** Os resultados sugerem que IDDDs para medicações tópicas podem ser importantes fontes de contaminação ou recontaminação da mucosa nasal de indivíduos em tratamento para condições do trato respiratório superior. Uma melhor compreensão dos riscos da reutilização de IDDDs após contato prévio com a mucosa nasal, melhorará as diretrizes sobre procedimentos de higiene e prevenção de riscos relacionados.

Descritores: Administração tópica, mucosa nasal, contaminação, bactérias.

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Introduction

Nasal congestion (the perception of reduced airflow or a feeling of fullness in the nose) is caused by a variety of environmental factors and diseases, including allergic rhinitis (AR). According to the International Phase III Study of Asthma and Allergies in Childhood (ISAAC), AR affects 14.9% of individuals aged 6-7 years and 39.7% between 13-14 years worldwide.[1] Allergic rhinitis usually causes nasal obstruction, a condition frequently perceived and described by patients,[2] and leads to self-medication.[3]

The nose provides easy access for delivery of medications and vaccines,[4] although the nasal vestibule is highly colonized and presents a potential risk for infection.[5] Nasal decongestants are among the most accessible and most frequently used treatments[6] and have high rates of self-medication in Brazil.[7,8] In general, they are widely sought due to their rapid efficiency in improving airflow through the nasal cavity[8] and generate a sense of well-being mainly in those individuals with a feeling of nasal congestion.[2,9] Usually this occurs in infections of the upper airways, as in allergic rhinitis, which affects about 29.6% of adolescents in Brazil.[10]

The nasal microbiota, even under physiological conditions, commonly presents bacteria such as *Staphylococcus aureus*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[11] It has been reported that nasal colonization by *Staphylococcus aureus* affects 20-30% of healthy individuals.[12] However, because of a weakened immune response, a pharmacologically suppressed immune system, or nasal mucosal contact with bacteria not recognized by the immune system ('not self', in immunology), bacterial proliferation is favored, allergic or non-allergic immune responses are activated, and inflammatory mediators like histamine and prostaglandins are released. This induces inflammatory cell recruitment, vasodilation, increased local permeability, and activation of goblet cells. These actions can lead to signs and symptoms such as edema, pruritus, nasal congestion, rhinorrhea, coryza, partial or total obstruction of airflow, and dyspnea.[13,14]

For the adjuvant treatment of these conditions, in order to promote mucociliary cleaning (which removes crystallized material from the nasal cavity), decrease the viscosity of the nasal mucus, and allow the return of airflow, hypertonic solutions (NaCl solutions), nasal decongestants (aromatic amines, aliphatic amines, and imidazole derivatives) and nasal topical corticosteroids (beclomethasone, budesonide, fluticasone propionate, mometasone, triamcinolone, fluticasone furoate, ciclesonide)[15] are frequently prescribed.

Topical medications with intranasal drug delivery devices (IDDD) have been widely indicated as possible therapeutics,[16] especially among patients with rhinitis (allergic or not), allergic rhinoconjunctivitis, rhinosinusitis, and nasal polyposis. In the specific case of rhinitis, glucocorticoids have been mentioned as the gold standard in improving patients' quality of life.[2,6]

IDDDs are frequent modes of treatment in both adults and children, mainly because they are considered a simple, effective, and safe treatment, especially from the point of view of risks related to the possible induction of lesions in the nasal mucosa by direct contact. Saline solutions, for example, have become popular as they are inexpensive, practical, and well-tolerated, although more studies are required.[8,17,18]

On the other hand, from the microbiological point of view, it is believed that IDDDs may not be safe, especially since during drug or saline solution delivery in domestic environments, direct contact between the face of the IDDD and the nasal mucosa can occur, which risks contamination and/or recontamination in the individual. To prevent this from happening, it is necessary that the user be properly instructed in relation to maintaining hygiene with the IDDD making direct contact with the nasal mucosa. However, these guidelines are scarce in the literature.

Taking this into account, the present study evaluated the possibility of contamination of an IDDD after simulating use in healthy individuals, with the intention of alerting the scientific community about the possible recontamination of the nasal mucosa of individuals being treated for conditions of the upper respiratory tract.

Materials and Methods

The in vitro experimental study investigated the possible contamination of an IDDD after single simulated contact with the nasal vestibule of healthy individuals. The study was carried out at the Laboratory of Microbiology and Biomorphology and Experimental Pathology of the University of Vassouras (Vassouras, Rio de Janeiro, Brazil) and the Laboratory

of Immunopathology and Experimental Pathology at the Center for Reproductive Biology (CRB; Federal University of Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil).

Subjects

A convenience sample was used in this study. We chose 14 healthy individuals, 12 men and 2 women aged between 18 and 24, who had no anatomical nasal abnormalities, no diagnosis of sinusitis, and no recurrent nasal bacterial infection or purulent nasal discharge. At the time of the study, none of the subjects were taking antibiotics. This information was collected from a semi-structured questionnaire specifically developed for this study. All individuals were instructed about all stages of the study and voluntarily signed a consent form. The study was carried out with the approval of the ethics committee (No. 1,596,547), according Resolution No. 466/12 of the National Health Council.

Sampling

Sealed packages containing a nasal solution of banzalconium chloride, sodium chloride, and nafazoline hydrochloride (Neosoro®; Neo Química, Rio de Janeiro) were opened 10 cm away from a Bunsen burner flame, while handling the bottles with a sterile glove. Immediately after opening each IDDD, an initial sample from the entire surface of the IDDD was collected with a sterile swab, soaked in 0.9% NaCl solution. After collection, the swab was immediately submerged in brain heart infusion broth (BHI). All subjects were instructed to insert the IDDD in the nasal ostium towards the limen nasi, and to maintain that position for 5 seconds without ejecting the medication, simulating the proper positioning of the device during medication use. Additionally, a second sample was collected following the same criteria mentioned for the swab collection of the first sample. A total of 28 samples (14 without contact with the nasal mucosa and 14 after contact with the nasal mucosa) were collected and incubated at 37ºC for 24 hours. After the samples were taken from the incubator, a first analysis of the culture broth appearance was carried out in order to identify the translucency of the broth and qualitatively examine the turbidity. The samples were then returned to the incubator at 37°C for a further 24 hours, and a second turbidity analysis of the broth was performed (Figure 1).

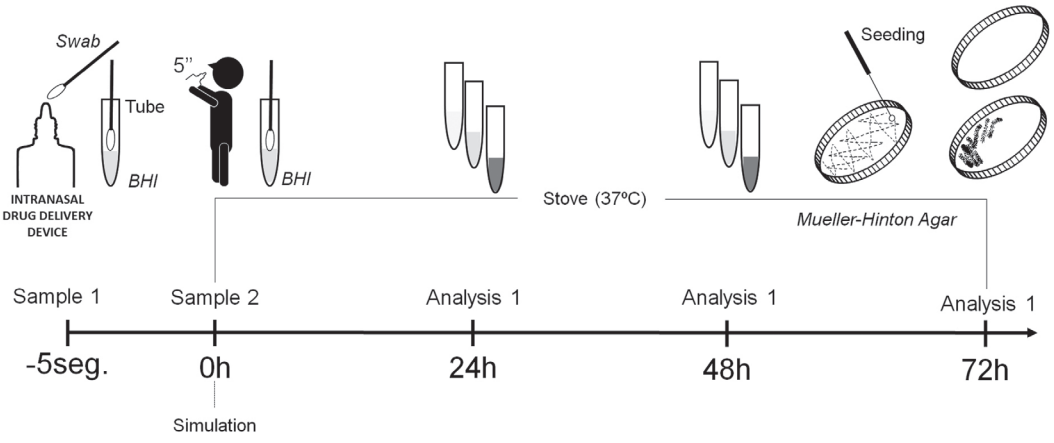

Figure 1

Experimental timeline. BHI - Brain heart infusion. '-5seg', '0h', '24h', '48h' e '72h' - respective times (in hours, "h", or seconds, "sec") in which each step was performed. '1ª collect' - At the beginning of the experiment (-5sec), intranasal drug delivery device (IDDD) samples were collected with sterile Swab, immediately after opening the package, and immersed in a tube containing BHI broth and kept in an incubator at 37ºC. '2ª collect' - Next (0h), IN samples were collected with sterile Swab immediately after the simulation of the IDDD use and immersed in a tube containing BHI broth and kept in an incubator at 37ºC. '1ª analyze' e '2ª analyze' - qualitative analysis of the turbidity of BHI broths. Within 48h the samples were seeded from Petri dish in culture media (Müller-Hinton agar). '3ª analyze' - qualitative analysis of bacterial growth

Furthermore, the samples grown in BHI broth were seeded in Müller-Hinton agar and incubated for 24 h at 37°C. After this period the plates were investigated for the presence or absence of bacterial growth. The plates were placed on a flat surface, kept at a fixed distance of 30 cm, and photographed (NIKON L810, 10 MP, 26x optical zoom, 4x digital zoom, 4608 x 3456 resolution, ISO sensitivity 80-1600) on a tripod in the same lighting conditions.

A descriptive analysis of 20 package inserts of nasal topical medicines registered in the National Agency of Sanitary Surveillance's (ANVISA) electronic system was carried out in order to identify information on: (1) guidelines on the correct positioning of an IDDD; (2) recommendations for IDDD hygiene; and (3) possible contamination of an IDDD.

Results

The BHI broth from the samples collected immediately after opening the intranasal drug delivery device without contact with the mucosa had a clear appearance after both 24h and 48h in culture, suggesting no bacterial growth. This result was later confirmed when the seeded samples did not demonstrate bacterial growth in a Petri dish after 72h.

From the samples that had contact with the nasal mucosa, turbidity was observed in the first 24 hours in 21.4% (n = 3) of samples. After 48h, this result was even higher, where 71.4% (n = 10) of samples had a turbid appearance. This result was also confirmed by bacterial growth on Müller-Hinton agar. (Chart 1e, Figure 2).

Twenty percent of the package inserts analyzed in the present study did not provide information on the positioning of IDDDs in relation to the patients' nostrils when describing recommendations for drug delivery. Although most package inserts had some recommendations regarding IDDD hygiene, 25% of them had no clear recommendations. Among the package inserts with no hygiene recommendations, there was at least a suggestion that IDDDs should not be shared in order to avoid contamination (Chart 3).

Discussion

In the current study, we tested the possible risk of contamination of IDDDs used in the treatment of upper respiratory tract diseases, as during application it can come in direct contact with the nasal mucosa, and this contact can be an important area of reinfection of the nasal cavity while re-using the IDDD.

We investigated the possibility of contamination because the guidelines on the correct positioning of IDDDs and hygienic procedures related to nasal instillation are unclear. We have shown, after simulating the use of IDDDs, a high risk of contamination among healthy individuals and confirmed inconsistencies in hygiene methods on the package inserts of these drugs.

Topically applied nasal drugs for patients with upper respiratory tract diseases are frequently prescribed8 and they are clinically required for facilitating the delivery of the active compound because the nasal vestibule is widely vascularized and presents a large surface area.[19] On the other hand, in order to achieve maximum efficiency, the pharmaceutical

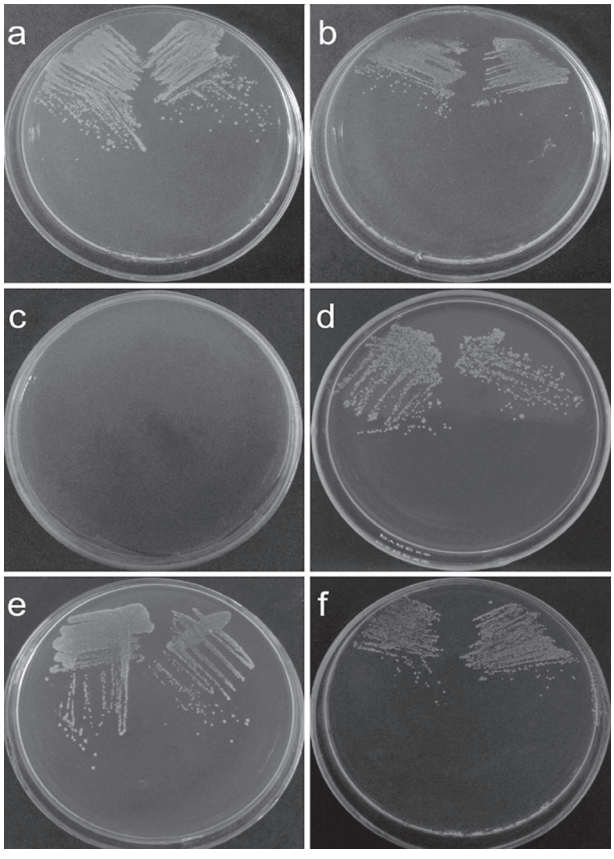

Figure 2
Petri dish prepared with Müller-Hinton agar culture medium were seeded from the 3 drops of samples collected after the simulation of the use of the intranasal drug delivery device in BHI liquid. Plates a, b, d, e and f resulted in visible bacterial growth

Table 1
Qualitative analysis of the turbidity of BHI broths from samples collected from intranasal drug delivery devices (IDDD) and bacterial growth results in Petri dishes

	Without contact with the mucosa			With contact with the mucosa		
Sample	**Swab (24h)**	**Swab (48h)**	**Petri dish (72h)**	**Swab (24h)**	**Swab (48h)**	**Petri dish (72h)**
1	Limpid	Limpid	-	Limpid	Turbid	+
2	Limpid	Limpid	-	Limpid	Turbid	+
3	Limpid	Limpid	-	Limpid	Limpid	-
4	Limpid	Limpid	-	Limpid	Limpid	-
5	Limpid	Limpid	-	Limpid	Limpid	-
6	Limpid	Limpid	-	Limpid	Turbid	+
7	Limpid	Limpid	-	Limpid	Limpid	-
8	Limpid	Limpid	-	Limpid	Turbid	+
9	Limpid	Limpid	-	Limpid	Turbid	+
10	Limpid	Limpid	-	Turbid	Turbid	+
11	Limpid	Limpid	-	Turbid	Turbid	+
12	Limpid	Limpid	-	Limpid	Turbid	+
13	Limpid	Limpid	-	Limpid	Turbid	+
14	Limpid	Limpid	-	Turbid	Turbid	+

BHI = Brain heart infusion; 24h, 48h, 72h = respective times in which the samples remained in the incubator at 37ºC. Petri dishes were prepared on Müller-Hinton agar and were seeded with 3 drops of samples in BHI broth; (+) There was bacterial growth; (-) There was no bacterial growth.

industry recommends regular use of topically applied nasal drugs[20] and there are reports that their efficacy depends on daily use.[21]

In fact, there is no consensus regarding the dosage or duration of treatment with topical nasal decongestants, including those that can be purchased without a prescription (except for those containing vasoconstrictors).[22] These factors may result in an increase in the number of times the IDDD contacts the nasal vestibule and raises the possibility of contamination and/or recontamination, increasing the risk to users.

Another factor that increases the possibility of contamination and/or recontamination is advice from pharmacists without adequate knowledge of the indications, contraindications, dosage, adverse effects, and possible drug interactions for the treatment of diseases - a fact routinely observed in Brazil in relation to respiratory diseases (Balbani, Sanchez, Butugan, 1996; Balbani et al., 1996).

There are no clear reports of risks associated directly with IDDDs. There is some evidence, however, that shows possible IDDD contamination

Table 2
Frequency distribution and χ^2 analysis of the number of samples according to the turbidity of BHI broths of samples collected from intranasal drug delivery devices and bacterial growth in Petri dishes

	Bacteria growth		
Aspect	**-**	**+**	**Σ**
Limpid	4	0	4
Turbid	0	10	10
Σ	4	10	14

χ^2 = chi-squared test. P = 0.0001.

Table 3
Recommendations on package inserts on the positioning for intranasal drug delivery devices (IDDD) and recommendations on the hygiene for the IDDD

Medication label	Positioning recommendations	Hygienic recommendations
Afrin®	"During administration, lean one head gently back and inhale during compression of the bottle. Extend your head and place one end of the bottle in each nostril without closing it completely"	–
Aznite	Apply the product to each nostril after doing the nasal hygiene. Keep your head straight to avoid unpleasant taste.	Clean the nozzle and replace the protective cap
Oxymetazoline hydrochloride	"With your head elevated, place the tip of the bottle into each nostril without closing it completely. During each administration, the patient should extend the head gently backward..."	–
Conidrin® 3%	Position the nozzle of the spray recipient facing up into the nostril.	Clean the nozzle and replace the protective cap
Fluimare®	Close one nostril with your fingers and position the end of the pump valve near the other nostril, keeping the bottle always upright	After administration, clean the pump valve with absorbent paper
Naridrin®	"... you should have your head gently extended back ..."	–
Nasoclean	Extend your head to the side and gently insert the end of the valve into the nostril.	Clean the applicator valve after use with a tissue or a dry cloth, cap the vial and store it in its original packaging.
Nasofar	Position the nozzle of the spray recipient facing up into the nostril entrance (do not insert the nozzle into the nostrils)	Clean the nozzle and replace the protective cap. The bottle should be stored inside the cartridge.
Nasofluid®	–	After use, wipe the applicator with a dry tissue and replace the protective cap.
Nasonex®	Close one of the nostrils, extend your head slightly forward and, holding the recipient upright toward the side of the nostril, insert the IDDD into the other nostril.	To clean the nasal applicator, remove the plastic cap and press the white ring gently upward, releasing the nasal applicator. Wash the applicator and the protective cap in warm drinking water and then rinse under running water. Let it dry in a warm place. Push the nasal applicator back into the bottle and attach the plastic cap.
Neosoro®	Position the nozzle of the spray recipient face up into the nostril (do not insert the nozzle of the vial containing the spray solution into the nostrils) and press the valve stem down. The head should be kept upright in a vertical position during application.	After use, wipe the applicator with a dry tissue and replace the protective cap.
Novo Rino®	–	–
Otrivina	Extend your head back (as much as you can) or if you're lying down, hang your head to the side.	Clean and dry nozzle before replacing the cap immediately after use.
Privina®	–	After use, the IDDD tube should be washed with warm water.
Rinofluimicil®	The eyedropper should not be introduced into the nostril.	Do not clean the dropper with water, but with absorbent paper, as the water accelerates the degradation of the medication.
Rino-Lastin®	Apply the product to each nostril after doing the nasal hygiene. Keep your head straight.	Clean the nozzle and replace the protective cap.
Rinosoro® SIC 3%	"Put the recipient in the nostril ..."	–
Sinustrat®	Position the nozzle of the spray recipient facing up into the nostril entrance (do not insert the nozzle of the spray bottle into the nostrils).	Clean the nozzle and replace the protective cap.
Snif 3%®	Press one of the nostrils with your index finger and in the other insert nozzle of the IDDD upright and press the applicator the number of times indicated by your doctor. Do not extend your head back at the time of application.	Rinse the IDDD and attach the protective cap.
Sorine	–	After use, wipe the IDDD with a dry tissue and replace the protective cap.

(-) There are no hygienic recommendations.

in the postoperative period of endoscopic surgery or the contamination of the liquid when inside the patient.[23]

Concerns about the risks associated with the use of nasal topical medications are generally not related to the hygiene procedures employed while handling and using nasal applicators. There are few reports on the need to sanitize the nasal vestibule as an adjuvant treatment.[21] Usually, the highlighted risks are those related to adverse effects of topical nasal medications, such as reduced milk production during breastfeeding,[24] risk of hypotension and bradycardia in elderly patients,[25] local irritation, bleeding, septal perforation, hypothalamic-pituitary-adrenal axis interference, ocular effects, growth effects, bone resorption, and cutaneous effects.[10]

Self-medication and abuse of nasal decongestants has been identified as an important risk factor due to drug-induced rhinitis by a rebound reaction.[26] In the literature, other reports point to an impairment of mucociliary clearance by the use of topical nasal medications.[27] In this case, impaired mucociliary dynamics lead to a favorable microenvironment for bacterial growth, increasing the possibility of IDDD contamination during direct contact with the nasal mucosa.

The present study has also shown that the package inserts of the analyzed drugs are not clear regarding the specific positioning of an IDDD. Concerns about the clarity of health descriptions, such as labeling and packaging patterns, have strong implications for therapeutic efficacy and patient safety, especially when such information comes from the internet.[28]

In general, studies that focus on investigating the relationship between the diameter, depth, and angle of the nasal spray position in relation to the anatomy of the airways restrict themselves to discussing only the information about the dose reached in the therapies,[4] but there are no reports of the possibility of contamination and/or recontamination of the applicator. New studies could clarify if ergonomic aspects can interfere in the contact area between an IDDD and the nasal mucosa, and consequently in the possibility of contamination and/or recontamination of the IDDD.

The risk of contamination was indicated in 75% of package inserts analyzed in the present study, both when considering the severity of the sharing of IDDD among users and when considering hygiene recommendations, although the information on the hygiene methods used is not clear. Therefore, there is no way to know if proper hygiene procedures are actually performed by the patients. Normally, when information is unclear and/or there is a low perception of risk by users, there is a lower tendency towards adherence to hygiene methods.[29]

Topical nasal medications are among the most common medications associated with self-medication3. It is known, however, that self-medication increases risk for the patient, and may have significant side effects.[30] In the present study, it was demonstrated that IDDD contamination is not easily predicted, since it requires specific culture techniques to identify bacterial growth. As could be observed, even with the guided use of IDDD by healthy individuals, there was a risk of contamination after a single simple simulation of the use of the nasal applicator and thus should be considered an important focus of possible recontamination of the upper airways.

In the present study, we were neither able to identify the bacterial types in vitro nor evaluate the rate of contamination of the IDDDs in contact with the nasal mucosa of individuals with previous upper respiratory tract infections. It is speculated that if an IDDD made contact with previously infected nasal mucosa, it could significantly increase the risk of contamination, although one study has shown that the variation of the microbiota between individuals was more important than the disease state.[11] If this latter point is considered on a large scale, better guidance on IDDD hygiene as well as guidance on how to re-use IDDDs should be treated as a public health problem, and this study suggests that preventive measures should be employed.

Environmental factors can affect the nasal microbiome, with potential effects on an allergic subject's health, resulting in a decrease in quality of life and increased nasal symptoms. Research implications suggest a new paradigm of hygiene for IDDDs. Whether IDDDs can alter the nasal microbiome or affect the course of inflammation in bacterial rhinosinusitis remains to be seen, and current therapeutic methods may need to be modified. However, further studies will be needed to clarify these issues.

Conclusion

Our results suggest that IDDDs for topical medications may be considered important sources of contamination/recontamination of the nasal mucosa of individuals who are being treated for conditions of the upper respiratory tract. A better understanding

of the risks of re-using IDDDs will help determine guidelines on hygiene procedures and prevention of related risks. Therefore, we recommend that hygiene and disinfection measures should be clearly patient-oriented, and that the use of nasal devices should be for individual use only.

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