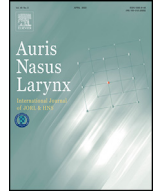




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# Survey of nebulizer therapy for nasal inflammatory diseases in Japan before and during the COVID-19 pandemic

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## ABSTRACT

**Objective:** Nebulizer therapy is an effective and safe topical treatment for rhinosinusitis and is frequently used by otolaryngologists in Japan. However, treatment methods used vary among regions and according to doctors' preferences. In this study, we aimed to investigate the use of nebulizer therapy for rhinosinusitis. Administration of nebulizer therapy has been affected by the coronavirus disease 2019 (COVID-19) pandemic. Thus, we also investigated the difference in the prevalence of nebulizer use before and during the pandemic.

**Methods:** Between February and September 2016 and in January 2021, we administered questionnaire surveys on nebulizer treatment for rhinosinusitis to otorhinolaryngologists, who were members of the Oto-Rhino-Laryngological Society of Japan, in Aomori, Saitama, Mie, Fukui, Shiga, Okayama, and Kagoshima prefectures.

**Results:** More than 90% of the otorhinolaryngologists performed nebulizer treatment for rhinosinusitis in 2016. In April 2020 (the first wave of the COVID-19 pandemic), the use rate decreased to 20%, but in January 2021, the use rate increased to 60%. Jet nebulizers were the most frequently used type. One-third of the otolaryngologists enlarged the natural opening of the paranasal sinuses in more than half of their patients by using vasoconstrictors. Cefmenoxime and betamethasone were the most commonly used antibiotics and steroids, respectively.

**Conclusion:** Because it is important to perform nasal pretreatment and strict disinfection of nebulizer equipment, it is clear that education of otorhinolaryngologists as well as paramedical personnel is required to ensure safe and effective use of nebulizer therapy in Japan.

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## 1. Introduction

Inflammatory nasal and paranasal sinus diseases, such as rhinosinusitis and allergic rhinitis, are common in daily clinical practice. Clinical treatment guidelines for acute rhinos-

**Table 1.** Questionnaire: Nebulizer treatment for rhinosinusitis.

Do you use nebulizer treatment for nasal diseases?
What type of nebulizer do you use?
For which diseases do you use nebulizer treatment?
What type of ancillary equipment do you use?
How often do you enlarge the natural opening of the paranasal sinuses in patients who undergo nebulizer treatment?
What drugs do you use in nebulizer treatment?
How often do you change the equipment? How do you wash, sterilize, disinfect, and dry the equipment?

inusitis have been published in Japan [1]; these guidelines recommend enlarging the natural opening of the paranasal sinuses before using a nebulizer for mild cases. Nebulizer therapy has become a well-known treatment option throughout Japan and has been covered by public health insurance since 1958. Nebulizer therapy is an effective treatment based on a drug delivery system to the nasal and paranasal cavities. The therapy effectively increases the local drug concentration by promptly and uniformly delivering drugs to a targeted local site. The therapy is safe with low systemic absorption and with few adverse reactions.

However, the method of administration varies among otorhinolaryngologists. Appropriate choice of devices, medicine and pretreatment are important considerations for nebulizer therapy in the treatment of rhinosinusitis.

Since there has been no uniformity in the methods of nebulizer therapy to date, otorhinolaryngologists have developed their own methods of use. Therefore, we investigated the current status of nebulizer therapy for nasal inflammatory diseases in Japan. As nebulizer therapy has also been affected by the coronavirus disease (COVID-19) pandemic, we also investigated the difference in the frequency of nebulizer use before and during the pandemic.

## 2. Materials and methods

We administered questionnaires on the use of nebulizer therapy for rhinosinusitis to members of the Oto-Rhino-Laryngological Society of Japan in Aomori, Saitama, Mie, Fukui, Shiga, Okayama, and Kagoshima prefectures from February 2016 to September 2016. The included questions are listed in Table 1.

In January 2021, we asked questions in the same prefectures of Japan. The first question was “Did you use nebulizer treatment in April 2020?”, and the second was “Did you use nebulizer treatment in January 2021?”.

Statistical analyses were carried out using the  $\chi^2$  test (Statemate V, 3B Scientific, Niigata, Japan).

## 3. Results

### 3.1. Participants

This study involved 414 otorhinolaryngologists from 94 hospitals and 320 private clinics. The final response rate to the questionnaires was 52.6%. The response rates for each prefecture were as follows: 29 (44.6%) in Aomori, 79(31.1%) in

**Table 2.** Frequency of nebulizer therapy use (%).

Prefecture	2016	2020 (April)	2021 (January)
Aomori	96.6	21.4	85.7
Saitama	94.9	21.8	61.3
Fukui	97.3	25.0	58.3
Mie	92.1	20.9	55.8
Shiga	92.1	17.1	48.5
Okayama	100	15.4	59.6
Kagoshima	98.2	29.0	58.1
Total	95.8	20.9**	60.6*,**

\*\* $P < 0.01$ , compared to 2016 by chi-squared analysis.

\*  $P < 0.01$ , compared to 2020 by chi-squared analysis.

Saitama, 38(54.3%) in Fukui, 83(77.5%) in Mie, 63(86.0%) in Shiga, 76(64.4%) in Okayama, and 38(57.0%) in Kagoshima.

### 3.2. Frequency of nebulizer therapy use for nasal inflammation diseases

In 2016, nebulizer therapy was performed by 95.8% of the otorhinolaryngologists. All otorhinolaryngologists in Okayama used a nebulizer to treat nasal inflammatory diseases. The lowest prevalence (in percentage) was observed in Shiga (92.1%). Aomori, Saitama, Fukui, Mie, and Kagoshima prefectures showed frequencies of 96.6%, 94.9%, 97.3%, 92.1%, and 98.2%, respectively (Table 2).

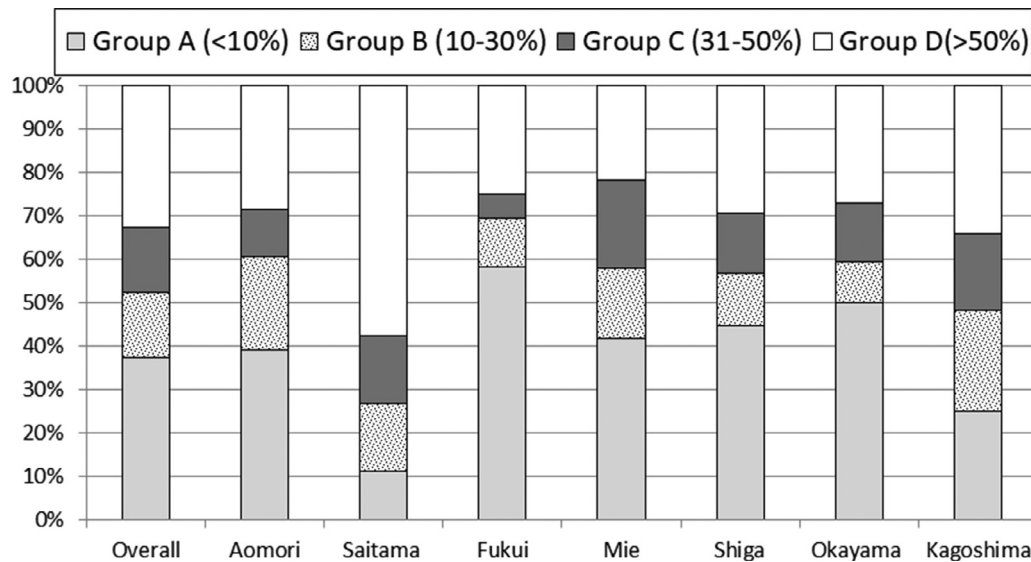
Seventeen otorhinolaryngologists did not use nebulizer therapy. Their reasons for not using nebulizer therapy were as follows. Five doctors believed that their clinics were understaffed to provide the treatment. Three doctors wanted to put more effort in performing surgery than in providing nebulizer therapy. Three doctors were not interested in providing nebulizer treatment, and three doctors believed that nebulizer therapy was ineffective for nasal inflammation. Three doctors also believed that nebulizer treatment was associated with a high risk of nasal infection.

In April 2020, nebulizer therapy was used by 20.9% of the otorhinolaryngologists. The highest frequency of use was found in Kagoshima (29.0%), and the lowest was in Okayama (16.0%). In January 2021, the treatment was used by 60.6% of the otorhinolaryngologists, and the lowest prevalence of use was found in Shiga (48.5%) (Table 2).

### 3.3. Types of nebulizers used

Jet and ultrasonic nebulizers were used in the ear, nose, and throat (ENT) clinics (ENT, Otorhinolaryngology) of the seven prefectures. Seventy percent of otorhinolaryngologists used jet nebulizers, which suggested that jet nebulizers were standard for ENT clinics. The ratios of the nebulizer device in each prefecture are listed in Table 3. The usage of ultrasonic nebulizers was higher than that of jet nebulizers only in Kagoshima (52.8%).

The devices were also classified by size into three types: installed, handy, and portable. The first is the drug-installed type, and the latter two (handy and portable) are drug-separate types. The drug-installed type was used more frequently than



**Fig. 1.** Frequency of enlarging the natural opening of the paranasal sinuses before nebulizer therapy. Among those who received nebulizer therapy, the doctors enlarged the natural opening in <10% of the patients in Group A, 11%–30% of the patients in Group B, 31%–50% of the patients in Group C, and >51% of the patients in Group D.

**Table 3.** Types of nebulizers used (%).

Prefecture	Jet type			Ultrasonic type
	Installed	>Handy	Total	
Aomori 78.8	15.1	93.9	6.1	
Saitama	74.9	8.2	83.1	16.8
Fukui	34.8	39.1	73.9	26.1
Mie	30.5	40.2	70.7	29.3
Shiga	41.3	17.3	58.6	41.3
Okayama	44.7	28.2	72.9	27.1
Kagoshima	10.2	27.2	47.2	52.8
Total	42.8	27.2	70.0	30.0

the drug-separate type (42.8% vs. 27.2%). Otorhinolaryngologists in Saitama and Aomori preferred the installed jet type, whereas those in Kagoshima alone preferred the drug-separate type.

### 3.4. Indications for nebulizer therapy

All otorhinolaryngologists performed nebulizer therapy for rhinosinusitis. Nebulizer therapy was also used for allergic rhinitis by 88.9% of the otorhinolaryngologists in the seven prefectures.

### 3.5. Ancillary equipment for nebulizer therapy

Mask and nosepiece types are ancillary equipment required for nebulizers. The nosepiece type was predominantly used over the mask type (82.7% vs. 17.3%). Nosepieces were made of plastic (59.6%), glass (38.1%), and silicone (2.3%) (Table 4). Plastic nosepieces were predominantly used in all prefectures, except in Mie, where glass nosepieces were the most frequently used (64.1%).

**Table 4.** Material types of ancillary equipment for nebulizers (%).

	Plastic	Glass	Silicone
Aomori	65.2	34.8	0
Saitama	90.2	9.8	0
Fukui	53.8	46.2	0
Mie	32.8	64.1	3.1
Shiga	59.0	39.3	1.6
Okayama	56.6	38.1	5.3
Kagoshima	62.9	33.8	3.2
Total	59.6	38.1	2.3

### 3.6. Frequency of opening the natural ostium into the paranasal sinuses before nebulizer therapy

Otorhinolaryngologists enlarge the natural opening of the maxillary and ethmoid sinuses before nebulizing a patient with sinusitis. However, this pretreatment was performed differently among otorhinolaryngologists. The otorhinolaryngologists were divided into four groups (groups A–D). Among those who received nebulizer treatment, the doctors enlarged the natural opening in <10% of the patients in group A, 11%–30% of the patients in group B, 31%–50% of the patients in group C, and >51% of the patients in group D. The percentage of otorhinolaryngologists in group A was 37.4%; group B, 15.1%; group C, 15.1%; and group D, 32.7% (Fig. 1). Saitama had the highest number of physicians who actively performed the opening procedures for the maxillary and ethmoid sinuses (group D: 57.7%). On the contrary, those in Fukui (group A: 58.8%) and Okayama (group A: 50.0%) were the most reluctant to perform opening procedures.

### 3.7. Medications for nebulizer therapy

Antibacterial agents were added to the nebulizer solution in 89.8% of all the ENT clinics. In Kagoshima and Saitama, 19.2% and 13.9% of the ENT clinics, respectively, did not use

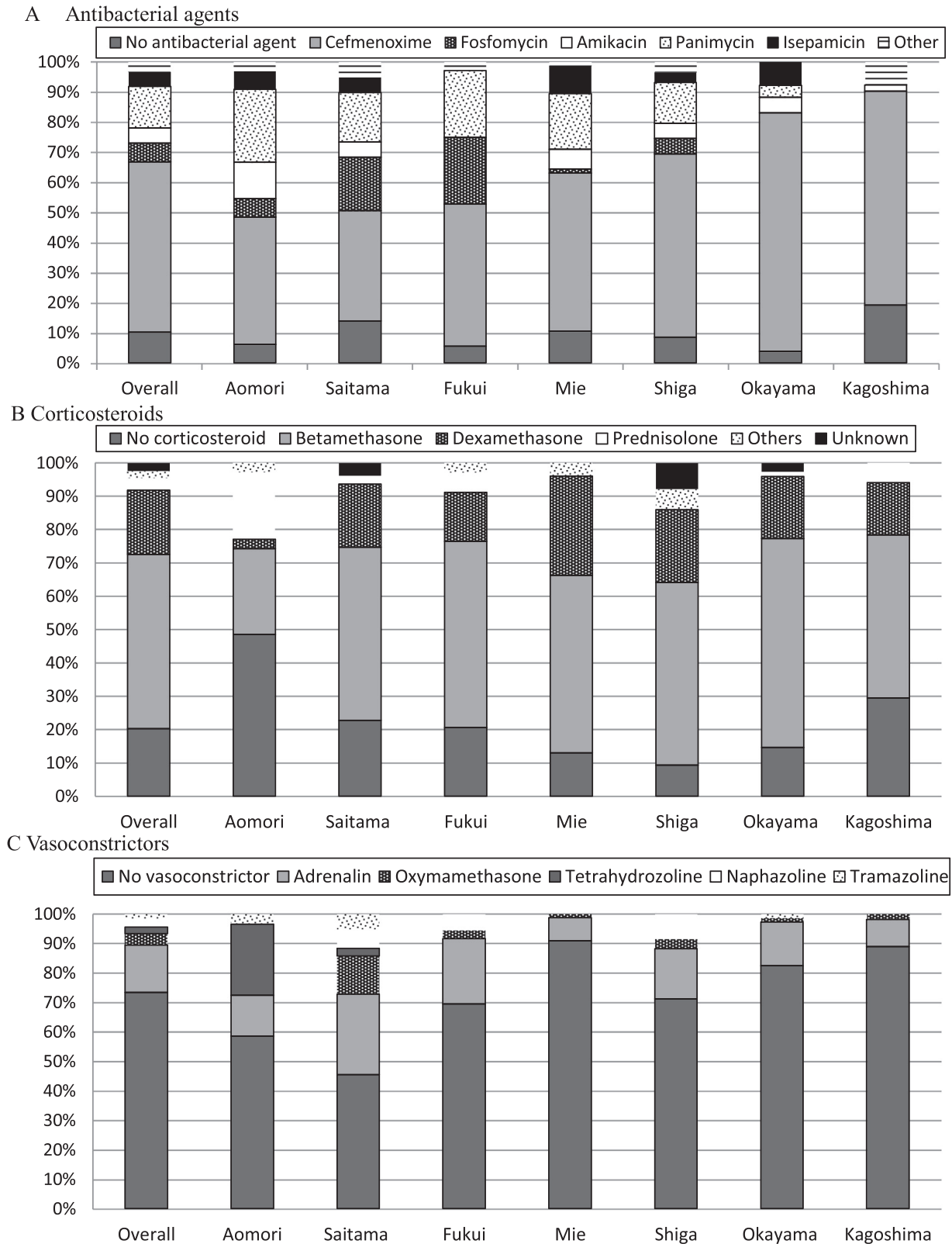
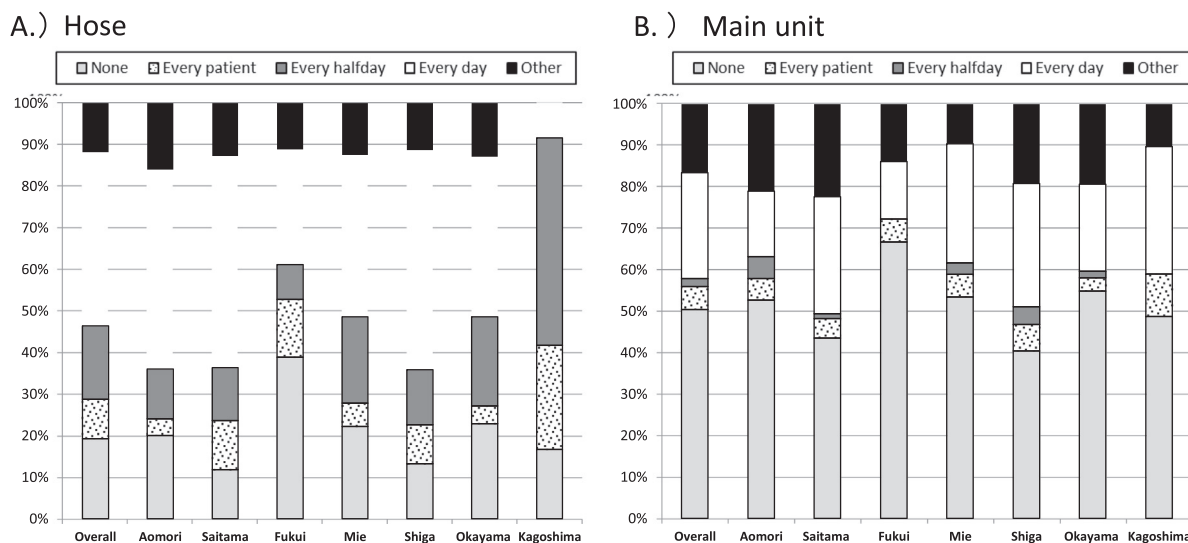


Fig. 2. Drugs used in nebulizer therapy. A) Antibiotics, B) Corticosteroids, C) Vasoconstrictors.

antibiotics (Fig. 2A). Cefmenoxime was the most commonly added antibacterial agent to a nebulizer solution in all prefectures. It was used in 79.2% of the clinics in Okayama and in 71.2% of the clinics in Kagoshima (highest rates among the prefectures). By contrast, the use rate in Saitama was

36.7% and that in Aomori was 42.4% (lowest rates among the prefectures). Panimycin was the second most commonly used agent (13.7%) in all prefectures. It was used in 24.2% of the clinics in Aomori, 22.2% in Fukui, 18.4% in Mie, 16.5% in Saitama, 13.6% in Shiga, 3.9% in Okayama, and



**Fig. 3.** Safety management. A) Frequency of disinfection and cleaning of hose, B) Frequency of disinfection and cleaning of the main unit.

0% in Kagoshima. These findings indicate that the type of antibiotics used differed among the prefectures.

Corticosteroids were also added to the nebulizer solution in 79.8% of the ENT clinics. Betamethasone, which was used in 52.3% of the ENT clinics, had the highest frequency of use, followed by dexamethasone (19.3%) and prednisolone (3.6%). Notably, one-half of the ENT clinics in Aomori did not use corticosteroids for nebulizer treatment (Fig. 2B).

Vasoconstrictors were used in 26.6% of the ENT clinics. They included adrenaline (16.0%), oxymethasone (3.9%), tetrahydrozoline (2.2%), naphazoline (3.0%), and tramazoline (1.5%). Vasoconstrictors were most commonly added in Saitama (54.5%), but they were least added in Mie (9.1%) (Fig. 2C).

### 3.8. Safety management: washing, sterilization, and disinfection of devices

Nosepieces and masks were disinfected after each patient use in 88.2% of the ENT clinics. Some ENT clinics used disposable nosepieces and masks. Disinfectants (67.5%), autoclaves (16.8%), boiling sterilization (4.2%), and gas sterilization (2.5%) were used to disinfect the nosepieces and masks.

Disinfection of hoses was performed in 68.9% of the ENT clinics daily (including every patient and every half day), whereas it was not performed in 19.2% of the ENT clinics (Fig. 3A). The main units were not washed or disinfected in 50.4% of the institutions (Fig. 3B). They were washed and disinfected after each patient in 5.5% of the institutions, every half-day in 1.9% of the institutions, and daily in 25.5% of the institutions. More than 50% of the institutions in Fukui (66.7%), Okayama (54.8%), Mie (53.4%), and Aomori (52.6%) did not wash or disinfect the main units.

Applying disinfectants (66.6%) was reported to be the most common practice for disinfection of the inner and outer hoses, followed by washing alone (18.8%) and autoclaving (7.4%) (Fig. 4).

## 4. Discussion

In this study, we confirmed the use of nebulizer therapy for nasal inflammatory diseases, such as sinusitis and allergic rhinitis, in Japan before the COVID-19 pandemic. More than 90% of the ENT institutions used nebulizer therapy; those not using nebulizer therapy were focused on palliative medicine and surgery. Nebulizers allow an effective and easy drug delivery to inflamed sinuses [2] and efficacy has been reported in European countries [3]. In recent years, efficacy as a postoperative treatment for endoscopic sinus surgery has been reported [4]. Also, nebulizer therapy has been considered to be a safe treatment without adverse events. However, therapy methods vary with regard to the drugs and equipment used. Nebulizer therapy is often administered as a customized treatment by each ENT clinic in Japan.

The three main types of nebulizers are jet nebulizers, which use compressed air, ultrasonic nebulizers, which use high-frequency piezoelectric quartz vibrations, and mesh nebulizers, which use the vibration of a microperforated mesh [5]. According to our study, jet nebulizers are used more frequently than ultrasonic nebulizers in Japan. However, the preferred type of nebulizer differed between regions, and ultrasonic nebulizers were used slightly more frequently in Kagoshima, Osaka prefecture. Jet and ultrasonic nebulizers differ in their aerosol generation, but their differences are not clearly elucidated. Previous studies reported that ultrasonic nebulizers can deliver more drugs to the paranasal sinuses than jet nebulizers because the former can generate smaller particles than the latter. However, recent developments in nebulizer devices have made this difference smaller [6,7].

In nebulizer therapy, the drugs should be delivered without waste to the target site and absorbed to exert their positive effects. To achieve this, patient's nasal tissues need to be prepared to absorb the drug. The presence of viscous nasal discharge prevents nebulized drugs from being absorbed at the target site, and obstruction of the middle nasal meatus reduces

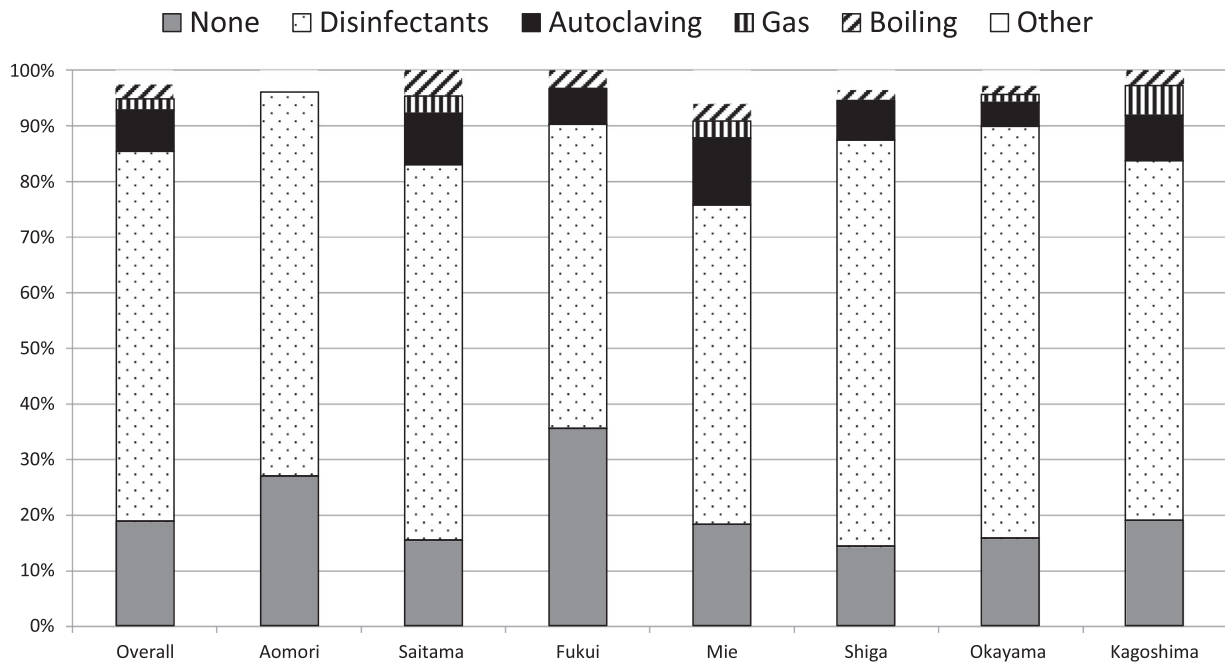


Fig. 4. Disinfection methods of the inner and outer hose.

the amount of drug that can reach the orifice of the paranasal sinuses or the middle nasal meatus. A previous study reported that a natural ostium of the maxillary sinus with at least 3 mm in diameter is required to allow the drugs to reach the maxillary sinus [2]. Therefore, nasal pretreatment, cleaning and opening of the natural ostium into the middle nasal meatus are important before initiating nebulizer therapy [8,9]. Therefore, we obtained information from the medical institutions about the percentage of patients who underwent opening of the natural ostium into the paranasal sinuses before undergoing nebulizer treatment. The results showed that 31.2% of the institutions performed this pretreatment in more than half of their patients. In some prefectures, pretreatment was carried out in 10% or fewer patients. Because it is recommended to enlarge the natural opening of the paranasal sinuses before nebulizer therapy, it is necessary to raise otorhinolaryngologists' awareness of this requirement for pretreatment. Various types of antibiotics have been used for nebulizer therapy. In Japan, cefmenoxime was approved for nebulizer therapy in 1996 and its use has increased in recent years. Betamethasone is the preferred steroid drug because of its stability over a long period of time.

The COVID-19 pandemic has affected the performance of nebulizer therapy in Japan. Aerosol-generating procedures include nebulizer treatment, as well as endotracheal intubation, bronchoscopy, and open suctioning. Some of these procedures, such as intubation, open suctioning, tracheotomy, manual ventilation, and bronchoscopy, can significantly increase the risk of bioaerosol production, possibly containing pathogens. Other procedures, such as nebulizer treatment, high-flow nasal oxygen, and use of medical aerosols, potentially disperse bioaerosols from the patient to the surrounding area, but no evidence exists on their additional potential to generate contaminated aerosols [10].

The viral pandemic of COVID-19 has raised concerns on the use of nebulization. Many guidances and statements have been reported for physicians on the role and use of nebulization in the current pandemic, based on current evidence and understanding [11]. Many of the reports are for lower respiratory tract disease.

There are many opinions about the use of nebulizer devices, but there is not much mention of the use of nebulizer devices for the upper respiratory tract such as nasal inflammatory disease. In our study, the use of nebulizer therapy was found to have decreased during the COVID-19 pandemic in Japan; the prevalence rate decreased to 20.9% during the first wave of the pandemic (April 2020). We believe that many medical institutions are resuming nebulizer therapy for nasal sinus disease while taking measures to prevent COVID-19 infection. Since the infection form of coronavirus is mainly droplet / contact infection, measures such as social distance, ventilation, disinfection of equipment, and other preventive measures are considered to be important. [12]

With regard to equipment management, nebulizers, which are heavily contaminated with microorganisms, are potential sources of infection. Therefore, they should be disinfected following proper procedures. Most medical institutions surveyed were private otorhinolaryngology clinics and disinfectants were used primarily for disinfecting equipment. Nosepieces and masks, which are directly attached to patients, were thoroughly disinfected. However, inner and outer hoses and main units were insufficiently washed, disinfected, and sterilized. Most bacteria detected on the nebulizer equipment are non-glucose-fermenting gram-negative bacilli, which form biofilms and are resistant to disinfectants [13]. Therefore, otorhinolaryngologists as well as paramedical personnel should be educated to appropriately disinfect the nebulizer equipment.

The limitation of this study is the low response rate, which may not reflect national results. However, in Japan, the region was selected in consideration of the difference in the incidence of COVID-19. I would like to make it an issue for future study.

## 5. Conclusion

Our investigation of the status of nebulizer therapy, which is commonly used for rhinosinusitis in Japan, before and during the COVID-19 pandemic, revealed several areas of concern. Because it is important to perform nasal pretreatment and strict disinfection of nebulizer equipment, it is clear that education of otorhinolaryngologists as well as paramedical personnel is required to ensure safe and effective use of nebulizer therapy in Japan.

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## Conflict of interest

The authors have no conflict of interest to declare.

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