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Consensus on methodology of experimental studies in rhinosinusitis – a narrative review

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Abstract. **Rhinosinusitis is one of the most common diseases today. Among diseases requiring treatment with antibiotics, it is the fifth most common. Acute rhinosinusitis is a significant medical problem that can significantly lower quality of life and can cause a large economic impact on society.**

Herein, we collected and analyzed data from several published studies regarding sinusitis with the aim of creating a sinusitis model. We included data from 786 studies published between 1996 and 2016 that came up on Google, Pro Quest Central or PubMed using the following keywords (or combinations thereof): "sinusitis", "rhinosinusitis", "experimental", "animal", "model", "rat", "rabbit", "guinea pig" and "mice".

An appropriate sinusitis model must be established using the correct animal. Thus far, sinusitis models have been published in rats, mice, and rabbits, with rabbits being the most frequently used animal. These animals are used because the anatomy and physiology of their sinuses are very similar to those of humans. While these animals can be used in surgical models, it must be noted that prolonged stress can cause them high mortality rates. Several studies have used strains of *Streptococcus pneumoniae* to induce rhinosinusitis; however, it has recently been shown that other pathogenic agents can be used for this purpose as well.

In this review, we presented several experimental sinusitis models in rats, mice, and rabbits. We hope that by presenting these methods, researchers may be better able to design and perform more useful sinusitis studies.

Key Words:
Rhinosinusitis, Animal model, Rats, Mice, Rabbits.

Introduction

Acute rhinosinusitis is an important disease that significantly decreases quality of life and has high economic impact on society[1,2]. Although there have been several studies published regarding rhinosinusitis, it is still the fifth-most prevalent disease requiring antibiotic treatment[3,4]. It is estimated that nearly 25 million people are afflicted with sinusitis every year in the United States alone, its treatment requires the collaboration of both general practitioners and otorhinolaryngologists. Because of its high prevalence and need for treatment by specialists, its economic impact is quite high[5,6].

While it is estimated that the prevalence of chronic rhinosinusitis (CRS) and acute rhinosinusitis (ARS) are quite high, it is hard to determine how many people are actually affected, some treat the symptoms on their own, without seeking help from a physician. It is estimated that 9% of all pediatric antibiotic prescriptions and 21% of adult prescriptions in the United States are for the treatment of rhinosinusitis; this adds up to approximately $150 million in prescriptions for sinusitis alone[6-8].

Several recent reviews[9] indicate that the innate immune system may play a role in the development of acute rhinosinusitis; because there was a significant difference in TLR9 expression in patients with allergic sinusitis when compared with patients with only allergies[10]. In addition, several recent studies[11] have shown that various PRRs, especially NOD-like receptors (NLRs), play a role in inflammation of the respiratory tract.

NLRs can interact with other proteins to form 'E protein' complexes, known as inflammasomes[12]; NLR inflammasomes can lead to the activation of procaspase-1, which causes the secretion of pro-inflammatory cytokines (e.g., IL-1β and IL-18)[3,13].

Bacteria are typically used to cause sinusitis in animal models. However, some models[14] use parasites, including pulmonary aspergillosis and non-invasive fungal sinusitis. Immunocompromised patients have high rates of mortality (50-80%)

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when they contract acute invasive fungal rhinosinusitis (AIFR), a very contagious disease[15,16]. In AIFR, the mucosa and submucosal structures of the paranasal sinuses or nasal cavity are overwhelmed with fungus and there is successive augmentation of the fungus into neighboring structures, including the vasculature, cranium, nasal delicate tissue, and orbit[17-19].

Treatment of rhinosinusitis is very difficult due to the disease's complexity. It can be affected by genetics, various pathogens (bacterial and viral), biofilms and bony and mucosal changes (e.g., polyposis and osteitis). Several published studies[6,14-19,20-61] using animal models of sinusitis, particularly those with acute rhinosinusitis or acute invasive fungal sinusitis, will be reviewed herein.

Methodology of the Review

In this review, we aimed to determine the best sinusitis model by reviewing several published studies. We reviewed all published studies that came up in PubMed, Pro Quest Central and Google with the following keywords (or combinations thereof): sinusitis, rhinosinusitis, experimental, animal, model, rat, rabbit, guinea pig and mice. Overall, 786 papers met these criteria and were reviewed for this paper.

Which Animal is Used in Sinusitis: Rat, Guinea Pig, Mice or Rabbit?

In humans, infection with rhinosinusitis quickly causes inflammation in the paranasal sinuses; successful animal models will replicate that effect. Animal models of sinusitis are typically used to determine the pathophysiology of this inflammation and to determine the most effective treatments. Unfortunately, some models of sinusitis can destroy the nasal passages and cause sinus drainage and blockages in the ostium[6,20-23].

Animal models of sinusitis are often problematic because of the way in which the animals are inoculated with the disease. Typically, animals are given sinusitis by first blocking the maxillary ostium with glue and then administering an infectious agent *via* sinusotomy. These techniques can damage the sinus divider and cause tissue irritation, which do not play a role in the pathophysiology of the disease but may influence the results[24].

Acute rhinosinusitis (ARS) in humans originates in the nasal region and obstructions caused by mucosal edema in the maxillary ostium are often reversible. In some animal models of rhinosinusitis, there is little control of the nasal hole; these are termed 'rhinogenic models', which are performed by wiping the pathogen into a nasal cavity. In this model, the sinuses remain intact, and the ostial blockage is reversible; therefore, rhinogenic models better reflect the pathophysiology of rhinosinusitis in humans[24-27].

Much research has been done using the sinusitis model in rabbits, as the physiology of their sinuses is quite similar to that in humans; however, they do have high mortality rates when under conditions of prolonged stress. Other animals used in this model are rats (Wistar and Sprague-Dawley), sheep and guinea pigs[6,28-30]. The majority of the reviews indicated that other pathogenic agents could be used in place of *Streptococcus pneumoniae*[6]. Again, the goal of a sinusitis model is to better understand the disease's pathophysiology in relation to human disease. All of the animal models used have their positive and negative aspects. However, the consensus is that rabbits are the best model, as their sinuses most closely resemble those of humans[31].

Rat Model of Sinusitis

Rat Model for Acute Rhinosinusitis

The method of Birdane et al[32]

In this model, a solution of bacterial *Staphylococcus aureus* (0.5-1 × 108 CFU/ml, Strain ATCC 25923) was administered intranasally with a dental needle, which was left in place for 72 hours. Any purulent nasal release was recorded and analyzed for the presence of *S. Aureus* by culture[32].

The method of Ye et al[33,34]

This model utilizes Merocel (Medtronic, Inc., Minneapolis, MN, USA) as indicated in the literature[33,34]. In the experimental group, Merocel sticks (2 x 3 x 20 mm) were inserted into the left nasal cavity and 0.1 mL *Streptococcus pneumoniae* was administered. The *S. pneumoniae* (a gift from the First Affiliated Hospital of Nanchang University Department of Laboratory Medicine) was diluted to 3 McFarland turbidities with sterile saline[34].

The method of He et al[35]

This model also utilizes Merocel strips for inoculation with *Streptococcus pneumonia*.

The method of Ge et al[36]

In this model, rats were anesthetized by intraperitoneal injection of 50 mg/kg sodium pentobarbital. Then, the nares were widened by making an entry point in the side of the left ala. A 1 × 2 × 18 mm Merocel stick (XOMED Surgical Products, Jacksonville, FL) containing *Staphylococcus* (strain 209P from the Japanese Collection of Microorganisms) was embedded into the left nasal cavity and remained there until perfusion. The hole was then sutured and the experiment continued[36].

Rat Model for Acute Invasive Fungal Rhinosinusitis

The method of Yan et al[14]

This model includes three steps. In the first step, the animals were administered cyclophosphamide (CPA, 75 mg/kg) and cortisone acetic acid derivation (CA, 80 mg/kg) both verified as safe and purchased from Sigma Aldrich[37-41] 5 days prior to receiving *A. fumigatus*. One day before receiving *A. fumigatus*, they were again given CPA at 60 mg/kg and CA at 80 mg/kg. In the second step, the right nasal cavities were embedded with Merocel wipes (Medtronic Xomed, Jacksonville, FL). In the third step, *A. Fumigatus* (strain AF9732, Peking University) was administered into the nasal cavities[14] and two days following, the rats received another injection of CPA (50 mg/kg) and CA (80 mg/kg).

The method of Zhang et al[42]

This model also includes three steps, but in a slightly different order than that by Yan[14]. In this model, the first step includes one-sided nasal obstruction with Merocel wipes, the second step includes the administration of cyclophosphamide (CPA), and the third step includes nasal inoculation with *Aspergillus fumigatus*[42].

Mouse Model for Sinusitis

Mouse Model for Acute Rhinosinusitis

The first bacterial mouse model for acute rhinosinusitis was introduced by Bomer et al[43] in 1998. In that model, mice were given *Streptococcus pneumoniae* intranasally.

The first model to inoculate mice with *Staphylococcus aureus* was introduced by Kiser et al[44], who described the dose dependence of *s. aureus* colonization *via* nasal tissue culture.

A rhinitis model for MRSA was introduced by Kruszewskal et al[45]; this model used hydrocortisone to suppress the immune response[45].

In the model by Schaffer et al[46], *S. aureus* was directly inserted into the nostrils, followed by administration of water containing streptomycin sulfate.

The method of Wang et al[3]

In this model, the mice were anesthetized with ketamine and chlorpromazine and then a slender glass tube was inserted into the right nasal cavity. Next, 10 µL *S. aureus* (1.2 × 109 CFU/mL) was inserted *via* an insulin needle[3].

The method of Jin et al[47]

This study included one control group and three groups of mice with wipes embedded into their right nasal cavities. The wipes contained either *Staphylococcus aureus* (MRSA COL), sterile saline or MRSA COL. Mice were sacrificed after 1, 4, 7 and 14 days, after which nasal lavage liquid was collected and cultured. It was found that only the mice given the *S. aureus* wipes had acute bacterial rhinosinusitis[47].

Mouse Model of Chronic Rhinosinusitis (CRS)

The method of Sautter et al[48]*, Lindsay et al*[49]*, and Khalid et al*[50]

In this method, mice were intraperitoneally administered *Aspergillus fumigatus* (AF) (Greer Laboratories Inc., Lenoir, NC, USA) with 2 mg of alum and 0.5 ml of phosphate buffered saline. Seven days later, the mice underwent another bilateral intranasal challenge with 5 µg of AF concentrate. The mice were treated this way 3 times/week for 3 months and then they were sacrificed[48].

The method of Tansavatdi et al[51] *and Lindsay et al*[49]

In this method, the mice were given *A. fumigates* (mixture of culture filtrate and mycelial concentrate, Hollister-Stier Laboratories, Spokane, WA, USA) intraperitoneally 3 times/week for 10 weeks to produce constant eosinophilic nasal and sinus inflammation[51,52].

Rabbit model of sinusitis

For the past fifty years, the rabbit model has been the predominant animal model of rhinosinusitis. Early rabbit models utilized the technique

of obstructing the natural ostium and administering bacteria down the anterior maxillary wall. This technique consistently induced non-rhinogenic maxillary sinusitis, but the animals underwent too much surgical manipulation with this model[53].

In 1997, Marks described the first rhinogenic model in rabbits. In this model, a bacteria-containing Merocel sponge (Medtronic-Xomed, Jacksonville, FL, USA) was inserted into the nasal cavity. This model has been used ever since[24].

Rabbit Model for Acute Rhinosinusitis

The method of Krespi et al[53]

In this method, rabbits were given acute bacterial rhinosinusitis (ABRS) by wiping the nasal cavity with a wipe containing pathogenic microorganisms[54].

The method of Campos et al[25]

In this method, bacterial rhinosinusitis was induced in rabbits by inserting a wipe into the nasal cavity, which contained streptococcal and staphylococcal toxoid. The wipes were removed after 10 days[25].

The method of Genc et al[54]

In this method, Merocel nasal sponges (Medtronic Xomed, Jacksonville, FL, USA) were inserted into the right nasal cavities. Then, *Streptococcus pneumonia* was injected into the sponges to induce rhinogenic sinusitis. The left nasal cavities remained untouched[55].

The method of Dolci et al[6]

In this method, Merocel nasal sponges were inserted into the right nasal cavities of the animals, followed by installation with streptococcal and staphylococcal toxoid (Toxoid pot®). The Merocel sponges were removed after 10 days. In every animal, the front maxillary sinuses were opened, and any secretions were collected and examined bacterioscopically[6].

The method of Guven et al[55]

In this model, the animals were inoculated with *Streptococcus pneumoniae* in the right maxillary sinuses; the left sinuses were left untouched[55].

The method of Wang and Shen[56]

This method included four groups of rabbits. One group was given only a nasal sponge, the second group was given a sponge inoculated with bacteria, the third group was given bacteria without a sponge and the fourth group was used as a control. For two weeks, the animals were examined with an endoscope and then the tissues were examined for histology and bacteriology[56].

The method of Chiu et al[57]

In this method, the maxillary sinus ostium of white rabbits was deterred with a pledget through an antrostomy made in the foremost face of the maxilla. The sinus was inoculated with *Pseudomonas aeruginosa* (PAO1) and after 7 days, the antrostomy was revived, the ostial impediment was evacuated, and a solitary lumen catheter was placed. Saline was irrigated through the catheter for 7 days in one group of rabbits, while a control group did not receive irrigation[57].

Rabbit Model for Chronic Rhinosinusitis

The method of Jia et al[58]

In this method, New Zealand white rabbits were incised vertically along the middle line of the nasal dorsum to uncover the anterolateral mass of the maxillary sinus, on which a 1.5-mm-hole was bored to enter the sinus cavity. Through the opening a bit of gelatin wipe was embedded and inoculated with a bacterial suspension. One to 8 weeks after the surgery, the sinus mucosa was harvested and analyzed *via* scanning electron microscopy (SEM) or hematoxylin and eosin (H&E) staining.

The method of Gocea[59] and Liang et al[60]

In this method, one-sided rhinogenic CRS was induced[59]. After anesthetization, rabbits were injected with PMA (Sigma-Aldrich, St. Louis, MO, USA) near the endoturbinates. The particular sides to be injected were randomly produced by a PC program[60]. Then, Merocel (Medtronic Xomed, Jacksonville, FL, USA) was embedded into the nasal cavity and was removed 15 days later. Liang et al[61] explained that this model can induce persistent inflammation for over 12 weeks, meeting the current definition of CRS.

Conclusions

In order to better understand human sinusitis, the appropriate animal model must be used[62]. Rats, mice, and rabbits have all been used in sinusitis models; however, rabbits are used the most frequently as their sinuses are quite similar to those of humans. However, they have high mor-

tality rates when exposed to prolonged stress. It is important to note that while the vast majority of studies have used *Streptococcus pneumoniae* to induce rhinosinusitis, some have used other pathogenic agents.

Conflict of Interest
The study was not funded by any company. There are no financial disclosures from the authors.

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Erkan Eski: Planning, literature survey, language editing, submission.
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