Case Report Rapport de cas

Ventral rhinotomy in a pet rabbit *(Oryctolagus cuniculus)* with an odontogenic abscess and sub-obstructive rhinitis

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Abstract — A rabbit was presented for severe dyspnea and was diagnosed with an odontogenic abscess obstructing the rostral nasopharynx using CT scan and oral endoscopy. The offending tooth was extracted intraorally, but due to persistent dyspnea, an endoscopic-guided ventral rhinotomy was performed. The dyspnea subsequently resolved, but the rabbit died 5 weeks later from a seemingly unrelated cause.

Résumé — Rhinotomie ventrale chez un lapin de compagnie *(Oryctolagus cuniculus)* atteint d'un abcès odontogène et d'une rhinite causant une subocclusion. Un lapin a été présenté pour une dyspnée grave et a été diagnostiqué avec un abcès odontogène bloquant le nasopharynx rostral par tomodensitométrie et endoscopie orale. La dent en cause a été extraite intra-oralement, mais, en raison d'une dyspnée persistante, une rhinotomie ventrale guidée par endoscopie a été réalisée. La dyspnée s'est subséquemment résorbée, mais le lapin est mort 5 semaines plus tard d'une cause apparemment non reliée.

(Traduit par Isabelle Vallières)

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Case description

A 1.5-year-old neutered male lop-eared rabbit *(Oryctolagus cuniculus)* was presented to the Ontario Veterinary College — Health Sciences Centre for chronic respiratory signs and dyspnea that had suddenly worsened over the previous 2 d. The owner reported open-mouth breathing, a right-sided rhinorrhea, and epiphora.

On physical examination, the rabbit was quiet, alert, and responsive. The rabbit weighted 2.6 kg (body condition score 4/5) and was over-conditioned. Mucous membranes were pink initially but rapidly became cyanotic after manual restraint with the rabbit displaying an orthopneic position with the head and neck extended. No ocular or nasal discharge was observed and abdominal palpation was within normal limits. On auscultation over the nasal cavities, increased respiratory noises were heard. Pulse oximetry revealed SpO_2 oscillating between 60% and 70% during restraint. The rabbit was placed in an enriched-oxygen chamber providing a PO_2 of 40% to 50% measured with an oxygen probe.

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Figure 1. Lateral radiographic view of a rabbit skull demonstrating a round, soft tissue opacity (black arrows) with a radiolucent center (white arrow) superimposed with the nasal cavity. Other abnormalities visible include mildly elongated reserve and clinical crowns of incisors, premolars, and molars, mild incisor malocclusion, mild clinical crown elongation of the peg teeth, and an apical lucency associated with an M3.

The following morning, the rabbit was sedated with midazolam (Versed; Roche Labs, Basel, Switzerland), 1.5 mg/kg body weight (BW), IM and butorphanol (Torbugesic, Zoetis, Kirkland, Quebec), 1 mg/kg BW, IM, for radiographs. Radiographs of the skull revealed mild incisor and cheek teeth malocclusion including mildly elongated reserve crowns of premolars, molars, and lower incisors, altered incisor dental plane, elongated peg teeth, and a rounded soft tissue opacity with a radiolucent centre superimposed with the nasal cavity (Figure 1). Thoracic radiographs were unremarkable. While the rabbit was sedated, blood was collected from the saphenous vein for a complete blood (cell) count (CBC), which was within reference intervals. A cursory dental examination using an otoscope was then performed. The right upper first premolar had a short clinical crown with mild corresponding point on its mandibular

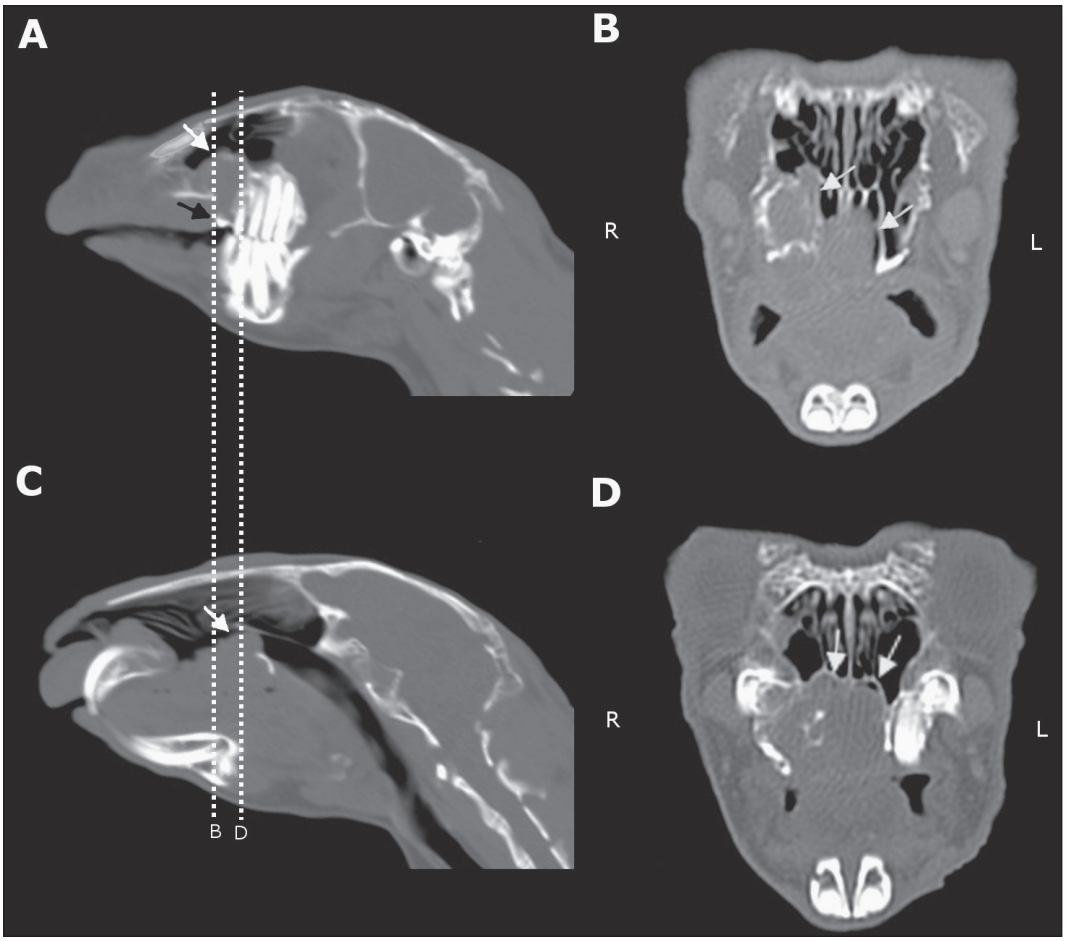


Figure 2. Computed tomography views of the head of a rabbit presented for dyspnea. A – Pre-contrast paramedian sagittal view, bone window (WW 2000/WL 350). The right rostral maxillary premolar (PM1) is mostly lysed with only a fragment of the reserve crown remaining (black arrow). Dorsal to PM1 is a visible abscess originating from the reserve crown and invading into the right nasal cavity (white arrow). B – Pre-contrast transverse image, bone window (WW 2000/WL 350). The abscessation is visible originating on the right side in the right maxillary recess (top white arrow) and extending medially into the rostral nasopharynx/caudal ventral nasal meatus (bottom white arrow) and right nasal cavity. C – Sagittal median view, bone window (WW 2000/WL 350). The abscess is clearly seen nearly completely obstructing the lumen of the rostral nasopharynx. D – Pre-contrast transverse image, bone window (WW 2000/WL 350). The abscess almost completely obstructed the airway at the rostral nasopharynx with only 1 to 2 mm of residual lumen (white arrows). White dotted lines on A and C represents transverse sections on B and D and are labelled accordingly.

counterpart. A deep nasal swab was taken from the left nostril for aerobic culture and sensitivity, which yielded no growth.

The initial therapeutic plan included enrofloxacin (Baytril; Bayer Healthcare, Mississauga, Ontario), 10 mg/kg BW, PO, q12h, metronidazole (Flagyl; Pfizer, New York, New York, USA), 20 mg/kg BW, PO, q12h, meloxicam (Boehringer Ingelheim, Burlington, Ontario), 1 mg/kg BW, PO, q24h, oxygen therapy, and Lactated Ringer's solution (LRS) at a maintenance rate (100 mL/kg BW per day) subcutaneously. While receiving oxygen, the rabbit's breathing and cyanosis improved, which correlated with a SpO_2 above 90%. The rabbit's appetite and fecal production were maintained with normal fecal pellet consistency and amount. Each time the rabbit was removed from the oxygen chamber for treatment, it became cyanotic, which resolved once it was replaced in the oxygenated enclosure.

On the third day of hospitalization, since no significant improvement of the breathing was observed, a CT scan of the head and neck was used to evaluate the upper airways. The rabbit was sedated with midazolam (1.5 mg/kg BW, IM) and butorphanol (1 mg/kg BW, IM), placed in ventral recumbency, and a 16 slice CT scan (GE Bright Speed; General Electric Healthcare, Milwaukee, Wisconsin, USA) was performed. Images were reformatted with routine bone and soft tissue algorithms. Slice thickness was 0.625 mm and images were reformatted into 1.25 mm slices. The field of view was 25 cm, kVP 120, mA 100. The pitch was 0.938:1 with a 1 s rotation time. Iopamidol (Isovue; Bracco Diagnostics, Princeton, New Jersey, USA), 2 mL/kg BW, IV, was administered via a 24 g IV catheter placed in the marginal ear vein. The CT scan confirmed the presence of a lesion and associated osteomyelitis of the maxillary bone at the level of the first maxillary premolar (PM1) on the right side (Figure 2). The tooth was almost completely lysed except for a fragment of the reserve crown embedded in the gingiva. Lysis of the surrounding alveolar bone of the

right maxilla and the palatine bone was also noted. The lesion was soft tissue/fluid dense and measured 10 mm × 12 mm × 12 mm. It extended into the rostral nasopharynx/caudal nasal ventral meatus from the right nasal cavity, its maxillary recess, and the premolar periapical area (1). There was a moderate contrast enhancement at the periphery of the lesion. The lesion, suspected to be an odontogenic abscess, almost completely obstructed the airway at the caudal aspect of the right nasal cavity and the rostral nasopharynx. Other differentials for the lesion included foreign body, cyst, and neoplasia. Other findings on the CT scan were similar to the skull radiographs and included reserve crown elongation of the mandibular and maxillary cheek teeth.

On the same day, after interpretation of the CT, the rabbit was induced with alfaxalone (Alfaxan; Jurox, Kansas City, Missouri, USA), 5 mg/kg BW, IV, and intubated with a 3.0 mm uncuffed endotracheal tube using the over-the-endoscope technique with a 2.7 mm, 30° angle rigid endoscope (Karl Storz Veterinary Endoscopy, Goleta, CA, USA), and maintained on isoflurane general anesthesia. End-tidal CO_2 was monitored with a pediatric main stream capnograph (Microcap; Covidien, Federal Way, Washington, USA); heart rate was monitored with a Doppler unit, and oxygen saturation was monitored using a pulse oximeter. An endoscopy-guided dental examination was performed using a 5 mm diameter 0 degree angle video otoscope (Karl Storz Veterinary Endoscopy, Mississauga, Ontario) with the rabbit placed on a dental table (Rodent table; Sontec Instruments, Centennial, Colorado, USA) and using a rodent cheek spreader (Rodent cheek dilator — large, Jorgensen Labs, Loveland, Colorado, USA). There was a lingual point noted on the right mandibular PM1 clinical crown due to lack of normal wearing since the corresponding upper right PM1 had no visible clinical crown. The tooth was trimmed using a diamond burr mounted on a low-speed rotating straight handpiece (XL-30W; Osada, Los Angeles, California, USA). Other premolars and molars appeared normal. The remnant of the right maxillary PM1 was visualized and removed with a dental scaler (Columbia curette 4R/4L; Sontec Instruments) using gentle debridement, as the CT scan had revealed that it was mostly resorbed and barely attached. Further debridement was performed in an attempt to remove more purulent material contained within the abscess (confirming the diagnosis of an odontogenic abscess). An aqueous 0.05% chlorhexidine solution was injected into the abscess pocket via a 24-gauge catheter to flush out purulent material. The airway was protected with a square gauze placed caudal to the site. Approximately 0.05 mL of medical honey (Medihoney; DermaSciences, Princeton, New Jersey, USA) was injected into the abscess with a 22-gauge catheter for its antibacterial properties (2). Buprenorphine (Buprenex; Reckitt-Benckiser, Mississauga, Ontario), 0.05 mg/kg BW, SC, was given twice q8h and meloxicam, 1 mg/kg BW, PO, q24h, were given for analgesia after the dental procedure (3–5) PO, q24h. Other treatments at this stage included syringe feeding with Oxbow Critical Care (Oxbow Animal Health, Murdock, Nebraska, USA), subcutaneous fluid therapy (LRS), oxygen therapy, and procaine penicillin G (Procaine Penicillin G; Dominion Veterinary Laboratories, Winnipeg, Manitoba).

There was no improvement after the dental procedure and it was decided that further surgical debridement was necessary. According to the topography of the abscess and nasal obstruction, and the rabbit's skull anatomy, an endoscopic-guided ventral rhinotomy approach was elected and performed 6 days after presentation.

The rabbit was sedated with midazolam, 1.5 mg/kg BW, IM, and hydromorphone (Hydromorphone hydrochloride; Wolters Kluwer, Baltimore, Maryland, USA), 0.1 mg/kg BW, IM. A 24-gauge intravenous catheter was placed in the marginal ear vein of the left ear and the rabbit was induced with alfaxolone IV titrated to effect (5 mg/kg BW, IV). The rabbit was intubated with a 3.0 mm cuffed endotracheal tube as previously described and placed under isoflurane general anesthesia. The rabbit's heart rate was monitored with a Doppler and an electrocardiogram (ECG), and ventilation was performed using a pressure controlled ventilator (Vetronics Small Animal Ventilator; BASi, West Lafayette, Indiana, USA). An arterial catheter was placed in the central ear artery of the right ear to directly monitor blood pressure. The rabbit received intravenous fluids (LRS 10 mL/kg BW per hour) and fentanyl citrate (Fentanyl citrate; Sandoz, Boucherville, Quebec), 10 μg/kg BW per hour, continuous rate infusion (CRI) for pain. The rabbit was kept on a heating pad throughout the surgery and the temperature was monitored using a rectal probe.

The rabbit was positioned in lateral recumbency. A rodent mouth gag (Jorvet) was used to open the mouth and a rodent cheek dilator (large) (Jorvet) was introduced into the oral cavity. A 30° 2.7-mm endoscope was used to visualize the oral cavity and guide the surgical approach. A small cavity was found in place of the dental extraction site with no purulent discharge. A number 15 scalpel blade was used to make a 1-cm incision midline on the hard palate over the palatal ridges centered just rostral to the first maxillary premolar and over the palatal fissure of the incisive/maxillary bones as per the location of the lesion on the CT images. The rostral rhinopharynx was penetrated and a small Meyerhoefer curette and a Frasier suction tip were used to expose, debride, and remove the abscessed tissues and purulent material under endoscopic guidance. Following debridement, the cavity, primarily composed of the rostral nasopharynx and right maxillary recess, was explored using the endoscope to ensure complete removal of the abscess and to lavage the abscess pocket (Figure 3). An 18-gauge catheter was used to flush the cavity with 0.9% NaCl under continuous suction. The walls of the abscess appeared to have been completely debrided and the turbinates were displaced but intact. Minimal to moderate blood loss was encountered. The site of the abscess was packed with approximately 2 mL of poloxamer 407 gel (Pluronic F-127; Sigma Aldrich, Oakville, Ontario) combined with gentamicin (Gentocin; Merck Animal Health, Madison, New Jersey, USA), 7.7 mg/kg BW, and cefazolin (Cefazolin sodium; Teva, Toronto, Ontario), 100 mg/kg BW, to achieve sustained release topical antibiotic therapy. The palatine soft tissue was sutured with 5-0 PDS (PDS polydioxanone; Ethicon, Somerville, New Jersey, USA) in a simple interrupted pattern. The purulent material retrieved from the abscess was submitted for aerobic and anaerobic culture and sensitivity, but no organisms were isolated.

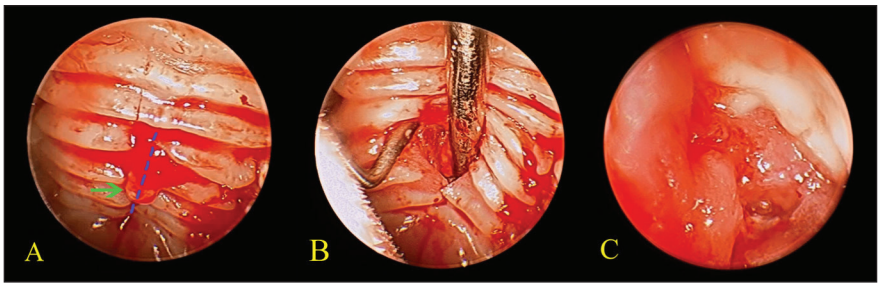


Figure 3. Intraoral intra-operative endoscopic pictures of a ventral rhinotomy being performed on a rabbit suffering from an odontogenic abscess extending into the nasal cavities using a 2.7-mm 30° angle rigid endoscope. A – A 15 scalpel blade was used to make a midline incision on the hard palate over the palatine fissure (dashed blue line). The normal transverse soft tissue palatal ridges are also clearly visible. Caseous purulent material is visible leaking from the abscess into the mouth via the incision (green arrow). B – A hooked probe and Frasier suction tip are used in conjunction to remove the caseous purulent material through the palatine incision. C – A visual inside the rostral nasopharynx obtained by passing the endoscope through the palatine incision. Note the white purulent material from the abscess still inside the nasal cavities yet to be removed.

The rabbit recovered without complication after the surgery and was maintained on fluids (Plasmalyte A and 2.5% dextrose), 10 mL/h, and the fentanyl CRI (2 μg/kg BW per hour) for 3 h after surgery. Since the dyspnea completely resolved after recovery from anesthesia, oxygen supplementation was discontinued. Only mild sneezing was observed that evening. The rabbit received buprenorphine, 0.03 to 0.05 mg/kg BW, SC, q6h, for pain control until the morning after surgery. The rabbit was syringe fed Oxbow Critical Care (Oxbow Animal Health) twice the day after the procedure (20 mL, then 25 mL). Fecal production appeared adequate, and the rabbit was continued on previously prescribed oral enrofloxacin, metronidazole, and SC penicillin G procaine.

The rabbit was discharged the morning of the 8th day of hospitalization (1.5 d after surgery). It was eating Timothy hay and lettuce on its own and fecal output was normal. It was sent home with metronidazole, 20 mg/kg BW, PO, q12h, enrofloxacin, 10 mg/kg BW, PO, q12h, meloxicam, 1 mg/kg BW, PO, q24h, penicillin G procaine, 80 000 U/kg BW, SC once every 3 d, and the owner was instructed to perform nebulizations with 0.05 mL amikacin (250 mg/mL) and 5 mL of Plasmalyte A for 15 min twice a day. A reevaluation was scheduled 1 wk later.

At re-evaluation, the rabbit was reported as having soft stools but was otherwise bright and alert with no apparent dyspnea. Oral examination under manual restraint did not identify any new findings. Nebulizations were continued but antibiotic therapy both parenterally and by nebulization were discontinued in case iatrogenic gastrointestinal dysbiosis was the cause of the soft stools. The stools improved thereafter. A week later, the rabbit experienced an episode of dysorexia and soft stools with mild to moderate gastrointestinal bloating. It was managed conservatively with supportive therapy that included metronidazole, 20 mg/kg BW, PO, q12h, buprenorphine, 0.03 mg/kg BW, SC q6 to 8h, simethicone (Gas-Z; Novartis, Dorval, Quebec), 40 mg PO once, subcutaneous fluids (LRS) at maintenance rate (100 mL/kg BW per day), and force feedings of Oxbow Critical Care as needed. While the rabbit did not exhibit any respiratory signs, a CT scan was still offered to re-evaluate the teeth and nasal cavity, but was declined due to financial constraints. The rabbit improved and was discharged 48 h later once it was eating hay. It was sent home on metronidazole, 20 mg/kg BW, PO, q12h, for 5 d and a buprenorphine oral suspension, 0.025 mg/kg BW, PO, q8 to 12h transmucosal for 3 d. Three days after discharge the clinical signs had resolved.

Three weeks later, the rabbit was presented to an emergency clinic for anorexia and lethargy. On presentation it was flaccid and unresponsive, with a normal heart rate, temperature, and respiration rate. No dyspnea was noted. The rabbit's last stools had reportedly been normal. The rabbit died at the emergency clinic the following morning from cardiac arrest due to an unknown cause. The owner declined necropsy; however, a post-mortem oral examination was performed with an endoscope. The teeth were unremarkable and the surgical site over the hard palate appeared to have healed well.

Discussion

This report describes the occurrence and short-term resolution of an obstructive odontogenic rhinitis using a minimally invasive endoscopic-guided ventral rhinotomy performed intraorally through the palatal fissure of the incisive/maxillary bones. To the authors' knowledge, this surgical procedure has not been reported in rabbits previously. Despite the death of the patient due to an unknown cause 5 wk after the surgery, the procedure was successful at immediately re-establishing normal upper airway patency, thus relieving the dyspnea, and allowed full debridement of the odontogenic abscess. Because of the short follow-up period, it is unknown whether the abscess would have recurred.

Odontogenic abscesses are common in rabbits with late-stage dental malocclusion but can occur at any stage (6–8). The pathogenesis of odontogenic abscesses involves food and bacteria being able to track up a loosened or broken tooth into the periodontal tissues and alveolar socket, resulting in the formation of an abscess associated with the maxilla or mandible (6,7,9). Odontogenic abscesses have been found to be comprised of a mixture of Gram-negative anaerobes (e.g., *Fusobacterium* spp., *Bacteroides* spp.), Gram-positive anaerobes (e.g., *Actinomyces* spp.), and Gram-positive aerobic cocci (e.g., *Streptococcus* spp.)

(6,10). These abscesses can extend to any structure of the head in close proximity to the dental reserve crowns and apical areas. While typically associated with a mandibular or maxillary cheek tooth, odontogenic abscesses are less commonly located in the retrobulbar area, nasal cavity, and other deeper structures of the head.

Treatment options for odontogenic abscesses include tooth extraction, surgical debridement of the abscess, injectable penicillins, antibiotic impregnated polymethylmethacrylate (AIPMMA) beads, or other antibiotic-impregnated materials (6,7). For aerobic bacteria, antibiotic therapy should be based on culture and sensitivity (6,7,10). For anaerobic bacteria, since most laboratories do not provide sensitivity, antibiotics with good anaerobic spectrum should be selected (e.g., metronidazole, penicillin, clindamycin, azithromycin) (6,7,10).

Rabbits are obligate nasal breathers and any obstruction of the upper airway may lead to severe dyspnea. Clinical signs of an obstructed nasal cavity include wheezing and increased respiratory effort (11). Rhinitis and upper respiratory disease can occur secondarily to dental disease such as odontogenic abscesses (12,13). Therapeutic options for odontogenic abscessation extending into the nasal and sinusal cavities of the rabbit are more limited than for standard odontogenic abscesses. Due to the inspissated nature of lagomorph pus, systemic antibiotic therapy is often insufficient to treat purulent rhinitis when a moderate to large amount of pus is present (14,15). Therefore, surgical debridement through a rhinotomy may be indicated (14,15). Dorsal and lateral approaches have been described in rabbits, cats, and dogs, and an intraoral palatal approach (ventral rhinotomy) has been documented in dogs, cats, and prairie dogs *(Cynomys ludovicianus)* for the treatment of nasal empyema of odontogenic origin or odontoma (14–17). In some cases, a urethral catheter is placed and secured in the rhinotomy site for continued treatment and flushing after surgery, or a temporary rhinostomy is performed (14,15).

When treating an abscess or an empyema through a rhinotomy approach, the surgical approach must be sufficiently extensive to accommodate the instruments used for debridement and curettage. Imaging including radiography, computed tomography, and rhinoscopy are useful to determine the extent of the rhinitis and to select the best surgical approach and location to better target the infected tissue and minimize iatrogenic trauma to the intranasal structures (14). The intraoperative use of a small diameter rigid endoscope may also allow magnification and a better visualization of the surgical site and nasal cavity in smaller patients such as companion exotic mammals.

Rhinitis and respiratory distress were present secondarily to the odontogenic abscess in this patient. This is different from previous cases of empyema in the nasal cavity, which involved diffuse accumulation of pus rather than walled off and circumscribed abscesses (14,15). Due to the topography of the odontogenic abscess causing the rhinitis and nasal obstruction in this rabbit, a dorsal rhinotomy approach was thought to be too invasive and would have induced unnecessary disruption of the nasal bone, dorsal nasal concha, and likely the ventral and medial nasal conchae. A lateral approach (pararhinotomy) through the perforated lateral surface *(facies cribrosa)* of the maxillary bone could have been performed as most of the abscessation was rostral to the premolars. However, it was determined to be more invasive than the selected ventral approach as it would have resulted in a deeper incision and the potential disruption of dental alveolar and apical structures. Despite there being no documentation regarding ventral rhinotomies in rabbits, an

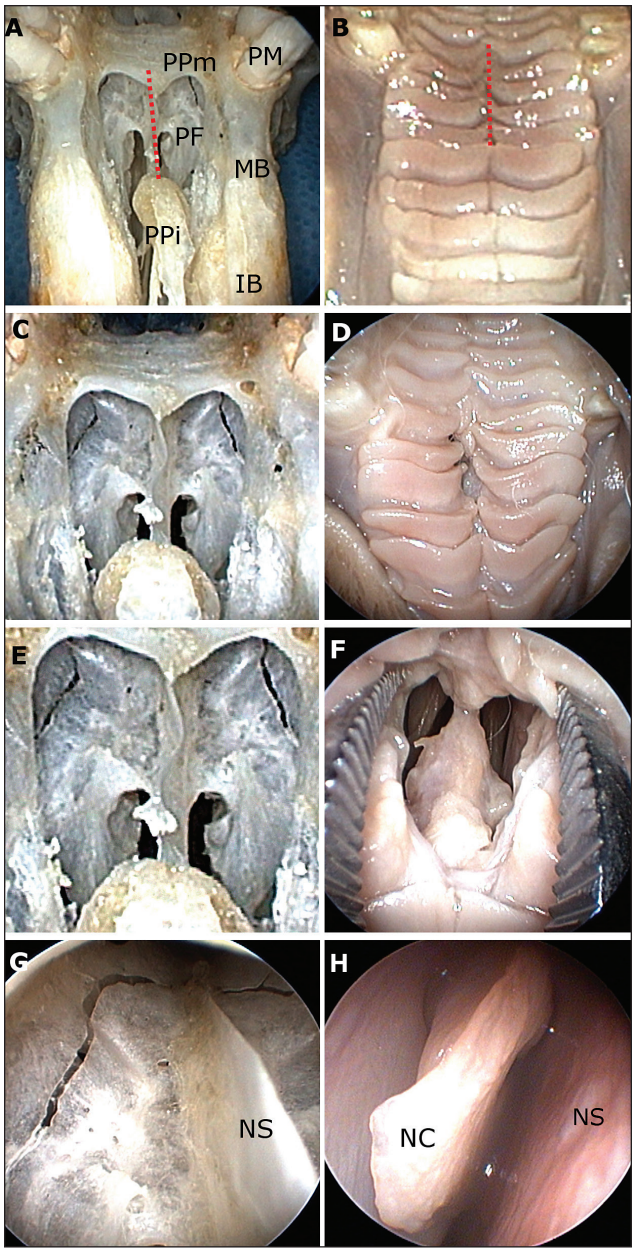


Figure 4. Surgical approach outlined on a ventral view of a rabbit skull (A,C,E,G) and a rabbit cadaver (B,D,F,H) as viewed through a rigid endoscope, the rostral aspect is to the bottom. A and B display the ventral intra-oral topographic anatomy (palatal surface). C, E, and G – the endoscope is further inserted into the palatine fissure with corresponding soft tissue views on D, F, and H. D – an incision on the hard palate over the palatal fissure was made as outlined on A and B (red dotted line). F – a mosquito forceps is used to open the surgical incision. G and H – the inside of the rostral nasopharynx is seen. PPm – palatine process of the maxillary bone; PPi – palatine process of the incisive bone; PM – premolars; PF – palatine fissure; MB – maxillary bone; IB – incisive bone; NS – nasal septum; NC – medial nasal concha.

intraoral palatal approach was selected based on the location of the abscess invading ventromedially from the right into the nasal cavity maxillary recess and the rostral rhinopharynx/caudal ventral nasal meatus (as demonstrated on CT scan), and the experience of the surgeon involved using this approach in dogs and cats. The palate of the rabbit, composed of the maxillary bone caudally and the incisive bone rostrally has a fenestrum, the palatine fissure, allowing a surgical incision into the nasal cavity via the palate without the need to perform an osteotomy or disrupt any other structures, making it the least traumatic option (Figure 4) (18). This novel surgical approach was minimally invasive and provided adequate access to the abscess for debridement while the use of endoscopic guidance allowed magnification and increased visualization. Potential disadvantages of a ventral rhinotomy approach in the rabbit include the reduced space in the rabbit oral cavity, and the inability to leave the incision open and marsupialize the abscess.

There is little documentation on the use of poloxamer 407 gel in veterinary medicine, especially in rabbits. Poloxamer gel is an amphiphillic material that is semisolid at room temperature and acts as an emulsifier, solvent, and lubricant for many drugs (19). Poloxamer gel mixed with a variety of antimicrobials has been used to treat rhinitis or dental abscesses in a few species, but this use has not been described in rabbits (20–22). There are reports of its use as a carrier agent for experimental drugs and models in the nasal cavities of rabbits, where it has been well-tolerated (20,23). In this case, it was used as a medium to slowly release antibiotics directly into the surrounding tissue as an alternative to creating a temporary rhinostomy or using a catheter to access the abscess site for repeated flushing post-surgery.

The minimally invasive, endoscopic-guided ventral rhinotomy approach allowed successful debridement of the abscess with immediate resolution of the dyspnea after surgery. The patient had a good recovery, was discharged less than 2 d after surgery and the surgical site healed without complication. The diarrhea seen at the 1-week re-evaluation and the subsequent hospitalization for dysorexia and diarrhea was suspected to be caused by dysbiosis. Oral and subcutaneous administration of antibiotics often leads to dysbiosis in rabbits. Inadequate amounts of fiber intake during recovery may also have contributed to the dysbiosis. The diarrhea resolved with supportive care and discontinuation of the antibiotics, supporting that presumptive diagnosis. The cause of the rabbit's sudden presentation of lethargy, anorexia, and its sudden death 5 wk after the surgery remain unknown. The postmortem endoscopic oral examination revealed minimal signs of malocclusion and a healed surgical site; it is therefore less probable that the sudden illness and death were caused by the initial dental malocclusion or rhinotomy procedure. However, in the absence of a complete postmortem examination, we cannot rule out that death occurred as a complication of the dental disease and periapical infection such as hematogenous infection or septic emboli. Furthermore, the subsequent diarrhea and dysorexia were managed conservatively and another underlying medical condition could not be ruled out. The death of this rabbit creates a major limitation in knowing the long-term success of this novel minimally invasive endoscopic-guided ventral rhinotomy approach, which should be further investigated with longer follow-up periods. CVJ

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