

Endoscopic dacryocystorhinostomy in acute dacryocystitis: a multicenter study in China

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Abstract

• **AIM:** To report the clinical profile, endoscopic dacryocystorhinostomy (En-DCR) management, and acute dacryocystitis (AD) outcomes in China.

• **METHODS:** Clinical data of 554 adult AD patients (554 eyes) who presented in 7 tertiary eye care centers for 10y from Jan 2010 to Mar 2020 were retrospectively analyzed. Clinical profile, En-DCR management, and outcomes of all cases were recorded. The anatomical and functional success were evaluated for 12mo post-operation.

• **RESULTS:** The analysis included 149 males and 368 females with a median age of 55.2y (range: 18-84y). There were 459 eyes with a history of epiphora or purulent secretion. The time between a symptom of lacrimal duct obstruction and acute onset was 1 to 540 (66.1±58.2)mo. Fifty-nine eyes had a history of the previous acute attack.

Seventy-four eyes developed a cutaneous fistula, while 11 eyes had post septal cellulitis pre-operation. En-DCR with an anatomical success of 91.7% and functional success of 90.1%. The success rate of the patients with a history of acute episodes and the preoperative fistula was lower than the overall success rates.

• **CONCLUSION:** En-DCR can be performed during an acute episode in AD with a success rate of over 90%.

• **KEYWORDS:** acute dacryocystitis; endoscopic dacryocystorhinostomy; lacrimal sac

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INTRODUCTION

Acute dacryocystitis (AD) is defined as “a medical urgency which is clinically characterized by rapid onset of pain, erythema, and swelling, classically below the medial canthal tendon with or without pre-existing epiphora mainly resulting from the acute infection of the lacrimal sac and perisac tissues”^[1-2]. The conventional treatment of AD includes warm compression, systemic antibiotics, anti-inflammatory, percutaneous abscess drainage, and external dacryocystorhinostomy (Ex-DCR) after resolution of acute infection^[3-4]. However, these conventional treatment approaches may result in several complications, including longer time for resolution, occurrence of cutaneous fistula, prolonged and recurrent infections, besides the risk of lacrimal reconstruction failure due to scarring, intra-sac synechiae, or organized granulation tissue within the lacrimal sac^[2,5-6]. In addition, the Ex-DCR results in a visible scar formation and may disrupt the medial canthal tendon complex, intimately involved in the normal lacrimal pump mechanism^[7-8].

In the last 2 decades, the advantages of applying endoscopic dacryocystorhinostomy (En-DCR) during the acute phase of AD have been recognized due to its rapid improvement in pain and inflammation. In addition, good exposure and opening

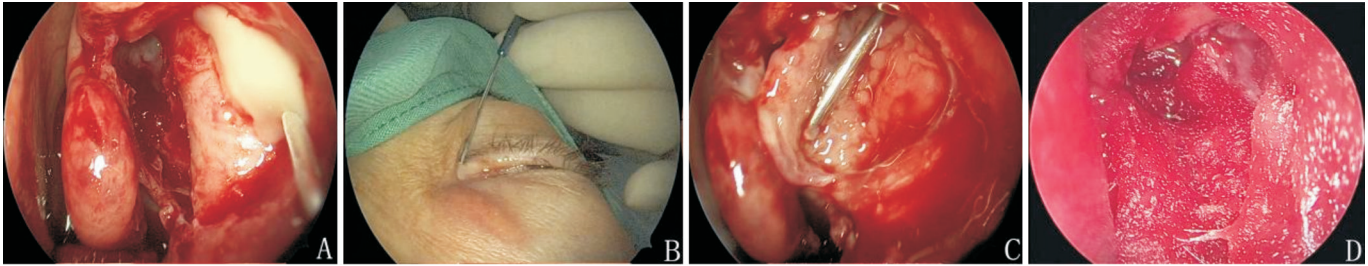


Figure 1 Intraoperative endoscopic views of the En-DCR in a patient with acute dacryocystitis A: An MVR knife was used to incise the inferior anterior portion of the lacrimal sac in order to release the purulent material therein; B: The medial wall of the sac was tented by inserting a Bowman probe through the superior punctum; C: An MVR knife was used to fully open the sac; D: Merogel infiltrated with dexamethasone was used to cover the ostial surface. En-DCR: Endoscopic dacryocystorhinostomy; MVR: Microvitreoretinal.

of the lacrimal sac on the nasal side could reduce infected and inflamed soft tissues without cutaneous traumatization. It can also preserve the lacrimal pump function, leading to the simultaneous treatment of sinonasal diseases^[9-11].

In various studies, En-DCR was applied in the acute phase of AD. However, most of these studies were case series in a local hospital with a small sample size and primarily focused on the outcome of treatment^[1-2,4-5,9]. Therefore, we aimed to carry out a multicentric study with a large sample size to analyze the features of clinical profile, En-DCR management, and outcomes of adult AD in 6 different provinces of China. In addition, we tried to identify the factors that might influence the postoperative outcomes.

SUBJECTS AND METHODS

Ethical Approval This is a retrospective study approved by the Institutional Ethics Committee (2023-065-K-53; Medical Ethics Committee, Wenzhou Medical University, Wenzhou, Zhejiang Province, China) and performed with the tenet of the Declaration of Helsinki. Written informed consent for participation was obtained.

The study was performed at the Eye Hospital of Wenzhou Medical University and Central Hospital of Lishui in Zhejiang Province, Eye Hospital of Nanchang University in Jiangxi Province, Renmin Hospital of Shiyan in Hubei Province, Eye Hospital of Ningxia in Ningxia Hui Autonomous Region, Eye Hospital of Wuhu City in Anhui Province, Baoan Central Hospital of Shenzhen in Guangdong Province from Jan 2010 to Mar 2020 aiming to evaluate AD carriers who were treated with En-DCR during the acute episode. The surgical procedures were carried out by eight surgeons. All surgeons had working experience with the same specialist (Wu WC) for at least 6mo.

Data recorded includes demographic profile, clinical history, duration of symptoms of acute attack, past medical intervention, examination findings, En-DCR management, outcomes, and complications. AD diagnosis at presentation in all patients was based on symptoms, signs of acute lacrimal sac inflammation with or without a history of past epiphora, and computed tomography.

En-DCRs were performed within 24h of admission. Broad-spectrum antibiotics were administered (ceftriaxone 2.0 g) half an hour before surgery for all AD patients as perioperative medication. Patients were excluded from this study if they were under 18 years of age, suffered from severe nasosinusitis, exhibited a history of traumatic obstruction, severe deviation of the nasal septum, primary nasolacrimal neoplasms, or systemic diseases resulting in bleeding disorders or coagulopathy. In addition, patients for whom data were missing or for whom the follow-up period was <12mo were excluded.

The operation was carried out under general anesthesia with the patient in the supine position. Under visualization with a 0-degree endoscope (Karl Storz, Tuttlingen, Germany), the lateral nasal mucosa was incised in the area of the lacrimal sac fossa by a blade. Underneath, the maxilla and frontal process were thinned by a power burr (Medtronic Xomed, Minneapolis, USA) and then removed by a Kerrison rongeur (Karl Storz, Tuttlingen, Germany). Next, an ultrasharp 9# microvitreoretinal (MVR) knife (Alcon, Fort Worth, USA) was used to incise the inferior anterior part of the lacrimal sac to release purulent material (Figure 1A). After checking the patency with saline irrigation *via* the superior punctum, a Bowman probe was placed through the superior punctum into the sac to tent the medial wall (Figure 1B). Finally, the knife was used to fully open the sac, guided by the probe (Figure 1C). After checking the patency with saline irrigation *via* the inferior punctum, the nasalmucosal flap was trimmed and repositioned to cover the exposed maxilla. Then Merogel (Medtronic Xomed, Minneapolis, USA) infiltrated with dexamethasone was used and packed around the wound (Figure 1D). Bicanalicular intubation was performed at the surgeon's discretion but generally in eyes with canalicular stenosis, a small scarred lacrimal sac, improper flaps, and a narrow upper nasal cavity. In addition, for patients with cutaneous fistula, fistulectomy was performed if the fistula is longer than 2wk, and no additional procedure is required if the fistula is shorter than 14d.

Postoperative care included intravenous ceftriaxone (2.0 g/d) for 2d. Intravenous methylprednisolone (20 mg/kg·d) was used for patients with orbital cellulitis for two days. Intranasal Rhinocort Aqua Nasal Spray (Astra Zeneca, Wilmington, USA) was used two times daily for 8wk in all subjects. In addition, topical antibiotics (0.5% levofloxacin; Santen Pharmaceutical Co., Ltd., Japan) and topical steroid eye drops (0.02% fluorometholone; Santen Pharmaceutical Co., Ltd., Japan) were used for 2wk. External signs of acute inflammation were evaluated daily in all subjects.

Postoperative follow-up time was set at 1, 2wk, 1, 3, 6, and 12mo after surgery. At each follow-up visit, symptoms of AD, epiphora and purulent discharge were recorded. The Munk scale was used to evaluate the symptom of epiphora^[12]. In addition, syringing and endoscopy exam with fluorescein test was done to assess the patency of the rhinostomy. The bicanalicular intubation was removed at 3mo postoperatively. Anatomical success was defined as the resolution of infection and a patent ostium on irrigation. Functional success was defined as resolution of infection and epiphora (Munk score was 0 or 1), free flow of dye in ostium on functional endoscopic dye test.

Statistical Analysis SPSS 26.0 was used for all the statistical testing. Demographic data were compared *via* independent *t*-test or Chi-squared test. The success rates were compared *via* Pearson Chi-squared test or Fisher's exact test. $P < 0.05$ was the significance threshold for this study.

RESULTS

A total of 554 patients (554 eyes) were recruited for this study, spanning over 10y from Jan. 2010 to Mar. 2020. All enrolled eyes were recommended for En-DCR during the episode of acute dacryocystitis. Twenty-one patients declined the surgery, and 16 patients failed to finish follow-up. Finally, 517 patients were included, with a mean age of $55.2 \pm 10.59y$. Three hundred and sixty-eight patients were females, and the other 149 were males. The clinical characteristics of these patients are compiled in Table 1.

Among these acute episode eyes, 459 eyes (88.8%) had a symptom of epiphora and/or purulent secretion. The mean duration of the symptom of lacrimal duct obstruction and the onset of AD was 66.1mo (ranging from 1 to 540mo). Fifty-nine eyes had previous episodes of an acute attack. Among them, 43 eyes had 1 acute attack, 11 had twice, and the other 5 had thrice or more. Twenty-seven eyes suffered acute attacks within 36h after lacrimal probing. In addition, 9 eyes had previous surgeries, including 6 with lacrimal tube intubation, 2 with Ex-DCR, and 1 with En-DCR.

Swelling in the lacrimal sac area and acute onset pain were the main symptoms of AD acute attack in all eyes. The time between the last acute attack and admission ranged from 12h to 4wk. At admission, 225 (43.5%) eyes had lacrimal abscess

Table 1 The clinical characteristics of AD patients

Variables	<i>n</i> (%); median±SE
Age	55.2±11.3y
18-30	15 (2.9)
31-40	24 (4.6)
41-50	102 (19.7)
51-60	195 (37.7)
61-70	150 (29.0)
71+	31 (6.0)
Sex	
Male	149 (28.8)
Female	368 (71.2)
Duration of epiphora to AD	66.1±58.3mo
1mo-1y	60 (13.1)
1y-3y	88 (19.2)
3y-5y	155 (33.8)
5y-8y	70 (15.3)
8y+	86 (18.7)
Previous acute attack	59 (11.4)
Fistula formation	74 (14.3)
Situation of AD at admission	
Abscess formation	225 (43.5)
No abscess formation	292 (56.5)

AD: Acute dacryocystitis; SE: Standard error.

formation (Figure 2A), while 292 eyes (56.5%) had no abscess formation with peridacryocyst infection or orbital cellulitis. All cases were treated with En-DCR within 24h of admission.

Fistula formation was one of the common complications after an acute attack of AD. Seventy-four eyes (14.3%) had fistula before surgeries (Figure 2B). Post septal cellulitis formation was another complication observed in 11 eyes (2.1%) prior to the surgeries in the study (Figure 2C, 2D).

Three hundred and forty-six eyes (66.9%) had completely relieved the pain on the first day after surgery. All cases reported complete relief in pain within 7d after En-DCR. The swelling was completely relieved within 14d after surgery. The erythema was completely relieved within 30d after surgery in all eyes (Figure 3). The duration of hospitalization was 3d in all cases.

Postoperative outcome for AD patients were compiled in Table 2. Anatomical success was noted in 474 (91.7%) eyes at a one-year follow-up. Eight eyes had persistent epiphora with anatomical patency existing, resulting in an overall functional success rate of 90.1% (466/517; Figure 4A, 4B). Among the 43 anatomical failed eyes, 37 presented with intranasal ostial closure, including 25 due to scar formation and 12 due to granulation formation (Figure 4C, 4D). In addition, 6 eyes presented with canalicular obstruction.

Eighty-four patients had bicanalicular intubation. Among them, 9 had a history of previous acute attack, 24 had cutaneous fistula, while 6 had both previous acute attack and cutaneous fistula. The anatomical and functional success rates were 79.8% (67/84) and 77.4% (65/84). The success rates of these

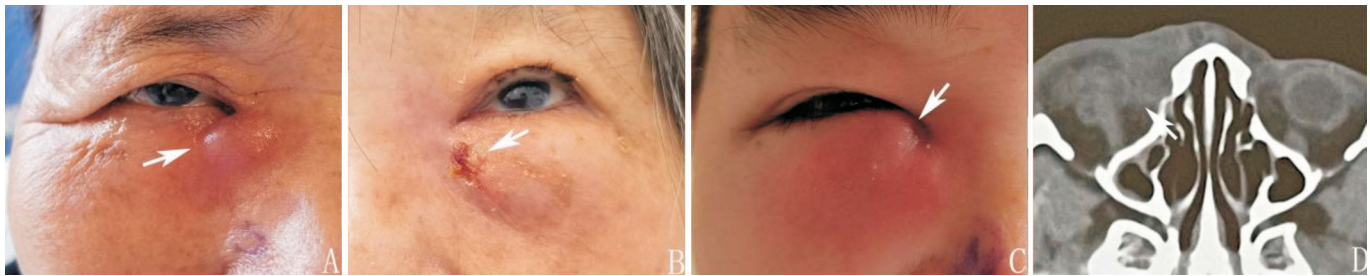


Figure 2 Complications after acute attack of acute dacryocystitis A: A patient exhibited lacrimal abscess formation (white arrow); B: A patient exhibited fistula formation (white arrow); C, D: A patient presented with preoperative post septal cellulitis, including evidence of acute external inflammation (C, white arrow) and acute inflammation exceeding the dacryocyst area into the orbital area (D, white arrow).

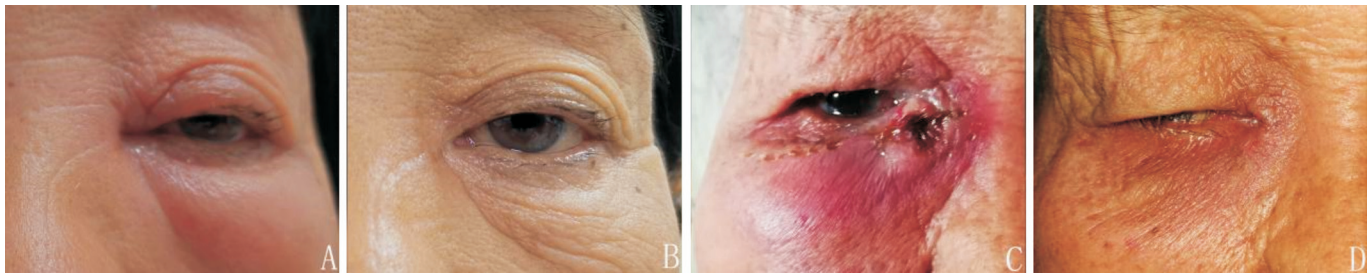


Figure 3 Resolution of acute inflammation after En-DCR A, B: A patient exhibited resolution of acute inflammation at 24-hour post-En-DCR; C, D: A patient exhibited skin fistulization preoperatively, and erythema was completely relieved 4wk postoperatively. En-DCR: Endoscopic dacryocystorhinostomy

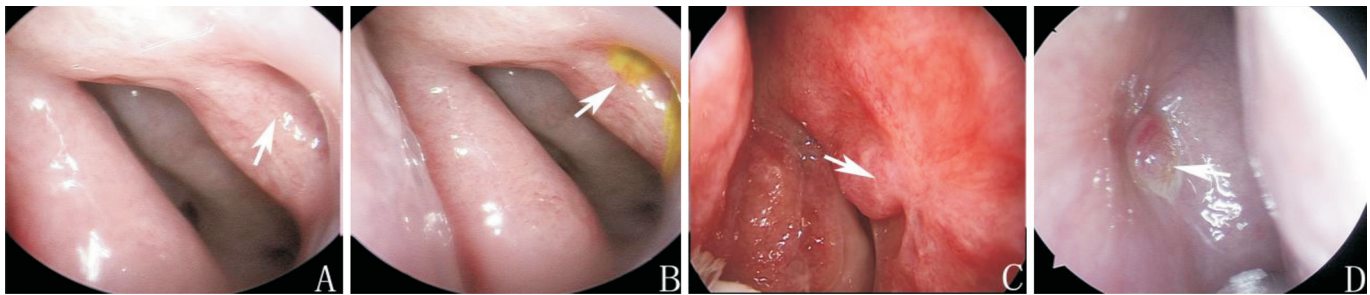


Figure 4 Endoscopic views outcome for acute dacryocystitis patients A, B: Endoscopic views revealing the success of free lacrimal system reconstruction; A: The left intranasal ostium remained patent and was covered by a mucosal layer exhibiting normal epithelial characteristics (white arrow); B: Normal functional endoscopic dye test results (white arrow); C, D: Endoscopic views exhibiting the failure of free lacrimal system reconstruction; C: A patient exhibited closure of the left intranasal ostium mediated by fibrotic tissue proliferation (white arrow); D: A patient exhibited right intranasal ostium obstruction owing to granuloma formation (white arrow).

Table 2 Postoperative outcome for AD patients

Parameters	Anatomical success rate	Functional success rate
Overall	91.7% (474/517)	90.1% (466/517)
Abscess formation	92.0% (207/225)	90.7% (204/225)
Without abscess formation	91.4% (267/292)	89.7% (262/292)
Intubaion patients	79.8% (67/84)	77.4% (65/84)
Previous episodes of acute attack	69.5% (41/59)	61.0% (36/59)
Fistuala formation	75.7% (56/74)	73.0% (54/74)

AD: Acute dacryocystitis.

patients were lower than the overall success rates (anatomical $\chi^2=11.426$, $P<0.05$; functional $\chi^2=11.423$, $P<0.05$).

For 9 eyes had previous surgeries, anatomical and functional success was achieved in 8 of the 9 patients. For 11 cases presented with post septal cellulitis, anatomical and functional success was achieved in 10 out of 11 patients.

For 225 eyes presented with lacrimal abscess formation, the anatomical and functional success rates were 92.0% (207/225) and 90.7% (204/225), respectively. No difference was detected between success rates in patients with lacrimal abscess formation and the overall success rates (anatomical $\chi^2=0.021$, $P>0.05$; functional $\chi^2=0.051$, $P>0.05$). The anatomical and functional success rates for 292 eyes without abscess formation were 91.4% (267/292) and 89.7% (262/292), respectively. No difference was detected between the success rates of patients without a lacrimal abscess and the overall success rates (anatomical $\chi^2=0.014$, $P>0.05$; functional $\chi^2=0.035$, $P>0.05$). In addition, the success rate was not statistically different between cases with and without abscess-forming (anatomical $\chi^2=0.053$, $P>0.05$; functional $\chi^2=0.126$, $P>0.05$).

For 59 eyes who had previous episodes of acute attack, the anatomical success rate was 69.5% (41/59), and the functional

success rate was 61.0% (36/59). The success rates of patients with previous episodes of the acute attack were significantly lower than the overall success rates (anatomical $\chi^2=27.542$, $P<0.05$; functional $\chi^2=40.102$, $P<0.05$). The anatomical success rate for 74 eyes who had fistula formation was 75.7% (56/74), and the functional success rate was 73.0% (54/74). Patients with preoperative fistula rates were significantly lower than the overall success rates (anatomical $\chi^2=17.150$, $P<0.05$; functional $\chi^2=18.039$, $P<0.05$).

There were no postoperative complications such as significant nasal hemorrhage, the spread of infection, or visual changes that occurred throughout the follow-up.

DISCUSSION

AD is a painful disease process characterized by acute suppurative inflammation of the lacrimal sac. AD is usually secondary to the virulent strain of bacterial overgrowth in the stagnant contents of the lacrimal sac at the background of naso-lacrimal duct obstruction (NLDO)^[2,5]. En-DCR allows an approach to the lacrimal sac through non-infected tissue planes and is free of the risks associated with Ex-DCR. Therefore, the use of En-DCR in the setting of AD is attractive, potentially allowing swift resolution of symptoms, reduced overall hospital time, and obviation for the need for subsequent lacrimal surgery^[1,6,11].

In this study, AD was more prevalent in middle-aged females (307 female cases between 40-65, accounting for 59.4% of the total cases), consistent with most other case series^[6,10]. Most eyes reported a history of a symptom of lacrimal duct obstruction before the acute attack. We found 88.8% of eyes had a history of epiphora and/or purulent secretion in this study. However, about 11.2% of eyes did not report any history of epiphora or pus before developing the AD. This absence of epiphora in a subset eye could be explained by the following reasons: First, dacryocystitis can be the first manifestation of a recent onset nasolacrimal duct obstruction. Second, patients with dry eye and tear hyposecretion may not complain of epiphora in the presence of nasolacrimal duct obstruction^[13].

There is no consensus on the relation of AD to previous treatment of lacrimal duct obstruction. However, a similar situation was reported among the major clinical series^[1,14]. In this study, 9 eyes had previous surgeries, including 6 with lacrimal tube intubation, 2 with Ex-DCR, and 1 with En-DCR. Anatomical and functional success was achieved in 8 of the 9 patients. However, due to the small sample size, further study is needed to confirm the relation of AD with previous lacrimal duct obstruction treatment. Furthermore, it is of concern that lacrimal duct probing may cause the onset of AD. In this study, 27 eyes suffered acute attacks within the 36h of lacrimal probing because of epiphora and pus. It may be related to the bacteremia caused by mucosal surfaces and

the dense endogenous microbial flora in those populations. Moreover, the infection presented in the lacrimal passage before probing may also promote the spread and proliferation of bacteria^[15-16]. Thus, lacrimal duct probing in patients with chronic dacryocystitis should be done cautiously.

Commonly, patients with AD are typically managed with systemic and topical antibiotics until lacrimal system inflammation progresses to the point of abscess formation before DCR is performed^[1,4,6,9,11]. However, ocular complications, including skin fistulation, cellulitis, and orbital abscess development, may occur while delaying surgery. Therefore, immediate En-DCR may be associated with early acute inflammation resolution, shorter therapeutic course, lower complication rates, and decreased intravenous antibiotic use^[1,2,9,11]. In the present study, 225 eyes had lacrimal abscess formation, and the other 292 eyes had peridacryocyst infection or orbital cellulitis without abscess formation. All these patients were treated with En-DCR immediately within 24h of admission. We achieved 92.0% and 90.7% success rates in anatomical and functional success in cases with abscess formation, while 91.4% and 89.7% success rates in anatomical and functional success rates in cases without abscess formation. No significant difference was observed in the success rate between cases with and without abscess formation. Additionally, no difference was detected between the success rate of cases with or without abscess formation and the overall success rate. Therefore, it can further be confirmed that En-DCR can be performed during the acute episode in AD with satisfactory results.

The satisfactory results achieved in the study may also be attributed to the modification of the lacrimal sac incision during surgery. Traditionally, a knife was used to release purulent material from the lacrimal sac after probing^[1,4,6]. In the study, the inferior anterior part of the sac was incised by a knife to release purulent material. Then the lacrimal duct was conformed to patency by syringing via the superior lacrimal canaliculi. Finally, the sac was fully opened by the knife guided by a lacrimal probe inserted through the superior punctum. These modifications were made for the following reasons. First, it is impossible to cannulate in patients with AD. However, cannulation can be performed easily if the lacrimal sac is decompressed. Furthermore, the above phenomena suggested that a valve or mucosal fold may exist at the common canalicular entrance^[17]. Second, canalicular/lacrimal sac mucosal folds (CLS-MFs) have been confirmed to be present in prior studies^[18-19], and large CLS-MFs can interfere with mucosal fold and orifice movement, ultimately blocking the common canalicular entrance. Therefore, releasing purulent material from the abscess to reduce the tension of the sac before implanting a probe could prevent damaging CLS-MFs. The necessity of tube intubation following En-DCR for AD

did not have a common consensus yet, with some in favor^[4,6], and others not applying^[20-21]. The possible complications of artificial lacrimal duct implantation are intranasal granulation tissue, peripunctal granulation, postoperative infection, canalicular laceration, and punctal adhesions^[22-23]. Silicone tubes were not used in patients in the present study other than in eyes with canalicular stenosis, a small scarred lacrimal sac, improper flaps, and a narrow upper nasal cavity. There were 84 patients with bicanalicular intubation, with an anatomical success rate of 79.8% (67/84) and a functional success rate of 77.4% (65/84). Of note, the success rates of patients with intubation were lower than the overall success rates. The relatively low success rate might be related to the lacrimal sac condition rather than intubation itself. Among the patients with intubation, 9 had a history of previous acute attack, 24 had cutaneous fistula, while 6 had both previous acute attack and cutaneous fistula. These two factors affecting postoperative outcomes are discussed below. Thus, prospective controlled studies on the effect of intubation should be conducted in patients with previous acute attacks and cutaneous fistula.

Merogel is an esterified hyaluronan derivative, which has been used as an anti-adhesive packing agent to stimulate mucosal epithelial healing in functional endoscopic sinus surgery^[24]. In addition, our previous studies^[25-26] have demonstrated that adjunctive use of Merogel may enhance the successful outcomes in En-DCR for chronic dacryocystitis. Of note, it promotes early re-epithelialization of the ostium, inhibiting the fibrotic tissues at the ostium and serving as a physical packing barrier for apposition of the lacrimal sac and nasal mucosa flaps. This study identified two factors that may influence the postoperative outcome. The first was a history of acute episodes, and the second was a preoperative cutaneous fistula. Previous episodes of acute onset of AD before treatment occurred in 59 eyes, and preoperative cutaneous fistula before the operation has happened in 74 eyes. The success rates of patients with previous acute episodes or with preoperative fistula were significantly lower than the overall success rates. In addition, a scar of dacryocyst mucosa and the narrow dacryocyst cavity was found in most cases with these patients at the time of the dacryocyst incision. Thus, intubations were implanted in some patients at the time of surgery to improve the success rate. However, the postoperative results were not satisfactory. Small scarred lacrimal sac and improper lacrimal flaps may be responsible for the lower success rate. We believe that immediate En-DCR at the time of acute attack may reduce rates of fistulization, in turn improving the success rate.

Since the attachment of the orbital septum to the posterior lacrimal crest limits the spread of inflammation to the posterior orbits, the inflammation of AD is typically limited by the dacryocyst, and peridacryocyst, as it presents a preseptal

infection^[27-28]. Only 11 cases presented with post septal cellulitis, and postoperative success was achieved in 10 out of 11 patients. However, in patients with post septal cellulitis, the length of hospital stay, the number of antibiotics used, and the hospitalization costs were increased^[6,10]. Due to post septal cellulitis is secondary to AD, and immediate En-DCR at the time of acute attack may reduce the rate of post septal cellulitis. Three hundred and forty-six eyes (66.9%) had completely relieved the pain on the first-day post-operation. All eyes reported completely relieving pain in the lacrimal sac region within 7d after En-DCR. The swelling was completely relieved within 14d after surgery. The erythema was completely relieved within 30d after surgery in all eyes. Similarly, pain relief and swelling resolution in patients with preoperative complications, including fistula formation and post septal cellulitis, were significantly longer than in those without preoperative complications^[27].

Forty-three eyes didn't achieve anatomical success in the study. The predominant causes of failure were ostium granulation, scar formation, and canalicular obstruction, similar to the previous reports^[4,10,27]. Postoperative epistaxis occurred in 7 patients and was resolved *via* the outpatient application of cotton packing soaked with a vasoconstrictive solution. Severe complications including orbital fat prolapse, orbital hemorrhage, visual changes, or sinusitis were not detected in either group in this study over the follow-up period.

Although we present the largest series and comprehensive clinical profile, En-DCR management and AD outcomes. There are multiple limitations to the present study. First, the exact mechanism of AD remains unclear, and it is not clear whether implantation of lacrimal probe before the tension of the sac is reduced will damage the CLS-MFs. Second, the necessity of tube intubation following En-DCR for AD remains uncertain. Additional researches are required to confirm these questions. At last, this study was performed using a specific technical protocol with patients presenting to tertiary care centers, which may represent a group with more severe pathology than the general population. This may limit applicability to a greater population.

In conclusion, through 517 AD eyes in this multicenter study, we found that the success rate of En-DCR during the acute episode with a surgical success rate of over 90%. In addition, we also found that the history of acute episodes and complications of the preoperative cutaneous fistula may reduce the postoperative success rate. As such, an immediate En-DCR may be adopted as the preferred treatment strategy for patients with new-onset AD.

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ML; Data collection: Yu B, Mao BX, Wang YH, Liu ZK, An NY, Jin HL, Wang ML; Analysis and interpretation of results: Yu B, Mao BX; Drafting the manuscript: Yu B, Mao BX; All authors reviewed the results and approved the final version of the manuscript.

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