Literature Review

Caustic esophageal injury in clinical settings

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ABSTRACT

Background: Esophageal stricture is loss of esophageal lumen patency and may involve injuries after ingesting caustic substances. Strictures may arise from acid reflux, medications, nasogastric tube insertion, infection and inflammation, radiation, or malignancy. Corrosive esophagitis is caused by ingestion of strong alkali or acid, usually causing tissue necrosis and underlying damage. **Purpose:** To review the clinical presentations, diagnostic modalities involved, treatments and outcomes, and complications of esophageal strictures following caustic injuries. **Literature review:** This systematic review involves original researches conducted between 2002-2022 indexed in PubMed and Europe PMC, using MeSH terms: "caustic injury" OR "caustic burn" AND "ingestion" AND "inflammation" following PRISMA algorithm. Biases were assessed using STROBE checklist and presented as narratives. **Result:** The search found a total of 326 literatures, out of which 16 studies were included in this review. Majority of caustic ingestion and esophageal strictures involving pediatric population was due to accidental ingestion. Alkali ingestion had more severe presentation than acid ingestion. Radiological imaging, including CT scan and MRI, could help in determining damages involved. Degrees of damages were related with mortalities or morbidities, and dilatation procedure might improve quality-of-life in some cases. **Conclusion:** Pediatric patients are at risk for accidental ingestions, and alkali ingestion creates more severe damage than acid. Radiological imaging may assist in determining involvement of underlying tissues.

Keywords: esophageal stricture, caustic injury, clinical outcome

ABSTRAK

Latar belakang: *Striktur esofagus adalah terjadinya sumbatan pada lumen esofagus setelah menelan zat korosif. Striktur bisa terjadi sebagai akibat refluks cairan bersifat asam, obat-obatan, pemasangan pipa nasogastrik, infeksi, peradangan, radiasi, atau keganasan. Esofagitis korosif disebabkan oleh karena menelan larutan asam kuat atau basa kuat, yang menyebabkan nekrosis jaringan dan kerusakan lapisan dasarnya.* ***Tujuan:*** *Untuk mengkaji gambaran klinis, cara-cara menegakkan diagnosis, penatalaksanaan dan hasilnya, serta komplikasi striktur esofagus akibat zat kaustik yang tertelan.* ***Tinjauan pustaka:*** *Dilakukan penelaahan artikel yang dipublikasi tahun 2002-2022, yang terindeks pada* PubMed *dan* Europe PMC, *menggunakan kata kunci: "*caustic injury" *ATAU* "caustic burn" *DAN* "ingestion" *DAN* "inflammation"*, sesuai dengan algoritma* PRISMA*. Penilaian terhadap bias dilakukan menggunakan daftar* STROBE*, dan disajikan sebagai narasi.* ***Hasil:*** *Ditemukan keseluruhan 326 kepustakaan, yang 16 penelitian diantaranya dapat digunakan dalam tinjauan pustaka ini. Kebanyakan kasus menelan zat kaustik dan striktura esofagus pada anak-anak disebabkan oleh ketidak-sengajaan. Luka bakar akibat menelan zat basa lebih parah daripada zat asam. Pemeriksaan*

radiologi, termasuk CT scan *dan* MRI, *dapat membantu memeriksa kelainan organ yang terjadi. Keparahan kerusakan jaringan berhubungan dengan mortalitas atau morbiditas, dan tindakan dilatasi bisa memperbaiki kualitas hidup penderita.* ***Kesimpulan:*** *Pasien anak-anak berisiko tinggi terjadinya menelan zat korosif tanpa sengaja, dan zat basa lebih parah akibatnya dibandingkan zat asam. Gambaran dari pemeriksaan radiologi dapat menunjang dalam menentukan kerusakan jaringan.*

Kata kunci: *striktur esofagus, luka bakar, hasil pengobatan*

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INTRODUCTION

Esophageal stricture is a loss of esophageal lumen patency (usually symptomatic when lumen is less than 15 mm in adults). Strictures may arise from acid reflux, medications, nasogastric tube insertion, infection and inflammation, radiation, or malignancy.[1] Corrosive esophagitis is caused by ingestion of strong alkali or acid, usually causing tissue necrosis and underlying damage. Alkali ingestion may cause liquefactive necrosis, while acid ingestion may cause coagulative necrosis.[2] Some commonly found household items, including detergent, drain cleaner, or rust remover may cause corrosive esophagitis.[3]

Thrombi found in necrosis restricts esophageal microcirculation, further worsening necrosis in inflamed esophagus. Bacteria exposure may cause additional inflammation and damage. Ulceration and granulation start from third day up to third week after exposure, characterized by slough formation and recruitment of inflammatory cells. After ulcerative phase, fibroblast infiltration and angiogenesis in granulating tissue may create weak spot and perforation risk is at its peak. Cicatrization and stricture forms after third week, when stronger connective tissue forms.[4] Due to common occurrence of esophageal stricture, this review aimed to explore clinical presentations, diagnostic modalities involved, treatments and outcomes, and complications of esophageal strictures following caustic injuries.

METHOD

PubMed and Europe PMC databases were searched on December 20th-December 23rd, 2022 using following MeSH terms: "caustic injury" OR "caustic burn" AND "ingestion" AND "inflammation". Our search covered papers from 2002-2022. After identifying prospective publications, each author independently screened and evaluated abstracts based on 2020 PRISMA guidelines. Each abstract was independently screened based on following criteria: 1) peer-reviewed studies in English; 2) original researches related to caustic injury after ingestion with associated inflammation in human subjects; and 3) full papers were available to access. Should any disagreement exist, all authors voted for inclusion after each individual author read the full paper. Following data were manually extracted: first author, year of publication, location of study, and presenting symptoms or outcomes. All data were individually verified, and presented as narratives as reported.

RESULT

The searches yielded 326 articles (with 6 duplicates being removed before screening). Abstracts failed to meet selection criteria

amounted to 191. After abstract screening, 129 articles were searched for full papers. Authors obtained 99 articles for second round of screening, then 72 articles were removed. In total, 16 articles were included in this review.

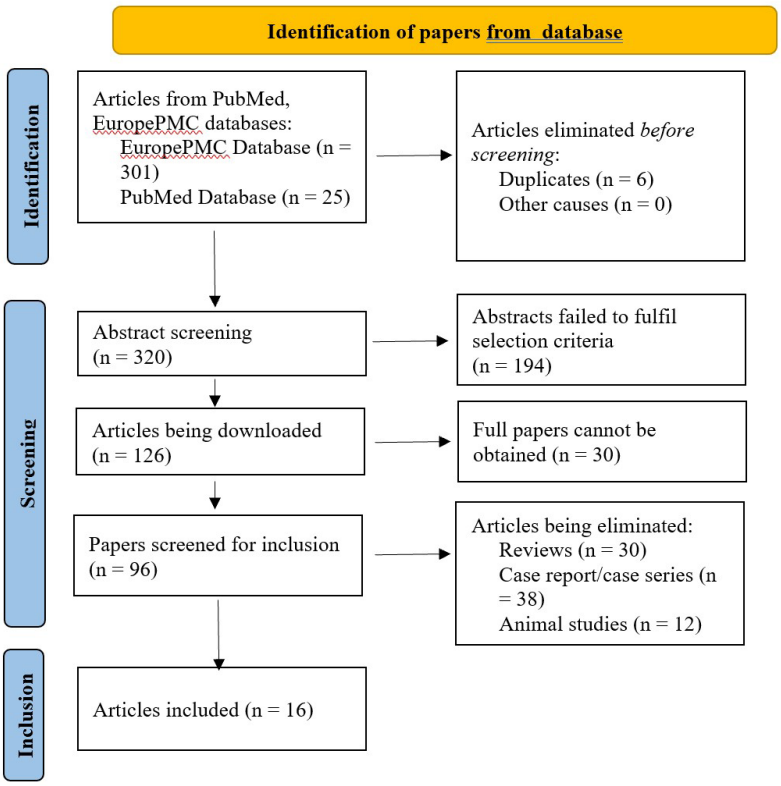

Figure 1. Systematic review algorithm based on PRISMA 2020[5]

Table 1. Summary of studies included in this review

No.	Author	Subject	Key findings
1	Okugbo *et al.*[6] 2020	49 patients with corrosive esophageal injuries	Corrosive esophageal stricture is debilitating, affecting more males (1.4:1), occurs mainly in pediatric population (mean age 4.7±4.8 years) old, requires multiple dilatations (38.8%) or esophageal replacement, and majority comes after accident (98%)
2	Ekpe&Ette.[7] 2012	Caustic ingestions in pediatric patients	Around 75% presented late, 25% suffered from short stricture and 18.7% suffered from long stricture, 50% were treated conservatively, 81.3% has satisfactory outcomes
3	Grey *et al.*[8] 2021	23 patients underwent MRI after button battery ingestion	Around 70% of patients were male, with median age 2 (0.94-17) years old, with 48% suffering from perforation, tracheoesophageal fistula, or spondylodiscitis; MRI is valuable to evaluate esophagus and surrounding tissues
4	Hollenbach *et al.*[9] 2018	31 patients with caustic ingestion esophageal injury	Alkalis creates higher mucosal injury severity (p=0.01) and more often related with suicidal intent (p =0.003)
5	Bahrami-Motlagh *et al.*[10] 2019	34 patients with upper GIT injuries after caustic ingestion underwent CT scan	CT scan can be sensitive in ruling out upper GIT mucosal injuries after caustic ingestion (sensitivity: 96.29%; specificity: 57.14%; K = 0.38), but grading requires endoscopy

No.	Author	Subject	Key findings
6	Mohammadi *et al.*[11] 2022	150 adult patients admitted to toxicology for assessment of caustic ingestion outcomes	Most common findings were grade 0 injury (40.7%), ingested depilatory agents (28.7%), intentional ingestion (72.0%), with mortality rate of 7.3%
7	Gelu-Simeon *et al.*[12] 2018	43 patients underwent upper GIT endoscopy after ammonia ingestion	Submucosal hematoma of gastric wall is common in ammonia ingestion (34.8%), should be distinguished from necrosis, and generally ammonia ingestion has favorable outcome (83.7% healed spontaneously)
8	Gvalani *et al.*[13] 2014	32 patients underwent antesternal colonic interposition for non-dilatable esophageal strictures	Antesternal colonic interposition for esophageal corrosive stricture is safe and effective (80% showed satisfactory function) with most common complication was cervical salivary fistula (18%)
9	Youn *et al.*[14] 2010	14 pediatric patients underwent endoscopic balloon dilatation for corrosive esophageal stricture	Limited cure rate for balloon dilatation in pediatric patients (14% successfully dilated), but outcome of repeated dilatation is sufficient for children to eat normally prior to surgical management (33% temporarily dilated successfully)
10	Cheng *et al.*[15] 2021	22 patients underwent esophagogastroduodenoscopy after caustic ingestion	Caustic ingestion produces mucosal damage and leads to excessive neutrophils (p=0.032) and inflammatory cytokines in peripheral blood with no difference in cumulative survival rate (p= 0.147)
11	Daniel *et al.*[16] 2020	30 patients with esophageal strictures underwent endosonography prior to balloon dilatation	Endosonography shows that corrosive and anastomotic strictures had greater depth of involvement compared to peptic stricture (3.51 ± 1.36 mm vs 1.39±0.62 mm; p= 0.026), and depth of esophageal wall involvement predicts dilatation response (2.14 ± 1.83 vs 5.80 ± 1.64; p = 0.001)
12	Aydin *et al.*[17] 2018	174 patients after esophageal caustic burn	The RDW parameter may lessen requirements for esophagogastroduodenoscopy, with cut-off above 12.20 shows increase of esophageal burns (84.2% sensitivity, 59.2% specificity, 38.6% PPV, 92.5% NPV)
13	Sharif *et al.*[18] 2022	492 pediatric patients with caustic ingestion	The PEWS > 6.5 better predict unfavorable outcome (94.4% sensitivity, 71.9% specificity, 89.3% accuracy), and DROOL < 6.5 predict esophageal injury (91.7% sensitivity, 72.5% specificity, 91.3% accuracy) in pediatric population
14	Isa *et al.*[19] 2021	46 pediatric patients underwent endoscopic dilatation for esophageal strictures	Endoscopic dilatations in pediatric patients are effective (98.8% success rate; 69.2% achieved complete response and 26.9% achieved satisfactory dilatation; median dilatation: 3 [IQR: 2-5]) and safe, but operator-dependent (p= 0.047). Non-anastomotic strictures require more dilatations
15	Canena *et al.*[20] 2012	30 patients underwent treatment for esophageal strictures using stents	Temporary placement of biodegradable stent of metal stent may help in providing long-term relief of dysphagia; polyester stent is undesirable due to migration (60%), reintervention need (20%), and lack of long-term improvement (10%). Further, longer strictures are more likely to reoccur.

No.	Author	Subject	Key findings
16	Mu *et al.*[21] 2020	21,840 patients with pesticides/ caustic ingestion and 21,840 healthy controls	Pesticide ingestion increases esophageal cancer risk (5.31 vs 1.66 per 10,000 persons-year; aHR: 2.52 [1.52-4.18]), while no significant difference is observed after caustic ingestion (1.14 vs 1.66 per 10,000 persons-year; aHR: 0.98 [0.29-3.33])

The researchers found 5 high quality studies, 4 moderately high-quality studies, 5 moderate quality studies, and 1 low quality study. Studies involved mainly lacked sufficient sample size, limiting generalizability. Further, majority of studies only involved single center, further hindering extrapolation to other populations.

DISCUSSION

Caustic injuries presentation and outcome

Pediatric patients below 5 years of age were more susceptible to accidental injuries caused by caustic ingestions, as shown by studies conducted in Nigeria (4.2±3.7 years old and 1-3 years old),[6,7] and USA (median age 2 years old).[8] Males were more common to suffer from caustic injuries, either accidental or deliberate, as can be seen on studies conducted in Nigeria (1.4:1 [p =0.024] and 4.3:1),[6,7] Germany,[9] United States,[8] and Iran (58.8% male).[10] The study in Germany also showed that majority of alkali ingestion was deliberate or accompanied with alcohol intoxication, while acid ingestion was more commonly caused by accident (76% vs 70%; p=0.003).[9] A study in Iran also showed that accidental ingestion was the most common cause of esophageal injury.[11] Interestingly, a study conducted in Guadeloupe showed that deliberate ammonia ingestion were more common in older (median: 49 years old) females.[12] An Iranian study also revealed similar older population (average age: 35.38±13.72 years); 88.2% ingested acid.[10] In India, 69% of patients deliberately ingested caustic substances, while 28% ingested caustic substances accidentally or attempted murder (3%).[13]

Most common alkali ingestions involved caustic soda (93.9% in a Nigerian study),[7] household cleaners (62% in German study),[9] hair removal cream, or sodium hypochlorite.[11] In a study in India, hydrochloric acid was the most common (60%), followed by sodium hydroxide (22%), and acetic acid or nitric acid (9% each).[13] Strong acids or acetic acid was the most common culprit of esophageal injuries.[9,14] Some folk antidotes given by first responders in Nigeria were palm oil (10.05%), raw eggs (12.2%), and anointing oil (8.2%),[6] and another study in Nigeria found that 75% of patients pursued immediate medical treatments.[7]

Esophageal injuries presentation varies. After ammonia ingestion, injuries ranged from grade IIA (27.9%), 0 (20.9%), I and IIB (14.0% each), and IIIA and IIIB (11.6% each). Further, 34.8% subjects showed submucosal hematoma, particularly in grade 0-IIA (p=0.02) or severe clinical presentation (p=0.01). Submucosal hematoma usually yielded better outcomes (89.3% suffered no stenosis nor death) although the difference is not significant (p=0.4).[12] Alkali ingestion presented in more serious condition (44% on grade IIIB, 19% on grade IIA, and 13% on grade IIIB), compared to acid ingestion (38% on grade I and IIA each, with only 24% on grade IIIA).[9] Higher grade of esophageal injury was associated with increased mortality; in one study in Iran, 83.3% of grade III patients died compared to lower grades (p=0.021).[1] In cases of esophageal injuries caused by battery ingestion, cervical location of battery is significantly related

with severe complications (p=0.026).[8] After caustic ingestion, severe esophageal damage showed higher neutrophils (84.2±10.0% vs 69.8±16.6%; p=0.032) and lower lymphocytes (11.0±9.1% vs 23.0±12.9%; p=0.013). Higher concentration of IL-2, IL-5, IL-8, IL-9, IL-12, IL-13, interferon-gamma inducible protein-10, macrophage inflammatory protein-1β, and TNF-α was higher, but did not significantly relate to survival rate (p=0.147).[15]

The CT-scan could be used to measure upper GI tract after caustic ingestion; in Tehran, Iran was found to be 96.29% (95% CI: 79.11-99.80%) sensitive, 57.14% (95% CI: 20.23-88.19%) specific, with 89.65% (95% CI: 71.50-97.28%) PPV, and 80.00% (95% CI: 29.87-98.94%) NPV to determine existence of esophageal caustic injury. Unfortunately, the extent of injury was difficult to determine solely by CT-scan; esophagoscopy was still needed for this purpose.[10] Meanwhile, in MRI, blooming artefacts ≥2 cm (p<0.001) and degrees of injuries seen on esophagogram (p=0.01) were associated with severe complications. Severe complications were related to prolonged hospital stays (p<0.001). Thus, MRI may be useful to help determine degrees of esophageal injuries due to better soft tissue contrast and non-invasiveness of MRI.[8]

Variable outcomes were found, but strictures or stenosis,[6,7,9,12,14] submucosal hematoma,[12] gastric outlet obstruction,[6] mediastinitis,[9] tracheo-esophageal fistula, spondylocystitis,[8] or perforation, and death[6–9,11,12] could be expected. In a German study, 19% of alkali ingestion cases suffered from esophageal stenosis and mediastinitis (10% and 0% on acid ingestion, p=0.52 and p=0.15). Mortality rate was higher on alkali ingestion (19% vs 10%, p=0.52), presumably due to more serious damage found.[9] Corrosive stricture had higher wall thickness compared to anastomotic or peptic stricture (3.51±1.36 mm vs 2.73±1.7 mm and 1.39±0.62 mm, p=0.026) and involved more wall circumference (76.38±26.2% vs 65.54±25.4% and 40.71±14.6%, p=0.021).[16]

Predictors of severity of caustic injuries and prognosis

In a Turkey study, red cell distribution width (RDW) <12.20 has lower risk for esophageal damages. Further, RDW is the most significant predictor of esophageal damage (p=0.000; OR 7.74 [95% CI: 3.02-19.9]). The RDW has 84.2% sensitivity, 59.2% specificity, 38.6% PPV, and 92.5% NPV for severe esophageal injuries.[17] Pediatric Early Warning System (PEWS) and Drooling Reluctance Oropharynx Other Leukocytosis (DROOL) score was studied in Egypt and Saudi Arabia as prognostic predictor in pediatric esophageal strictures. Median PEWS in good outcome group was 3 (1-8), while median PEWS in poorer outcome was 13 (9.3-17) (p<0.001). The median DROOL score in good outcome group was 8 (6-10), compared to 2 (1-4) in poorer outcome (p<0.001). The PEWS cut-off for poorer outcome was 6.5 (94.4% sensitivity, 71.9% specificity, 27.2% PPV, 99.1% NPV, and 89.3% accuracy). The DROOL score cut-off for poorer outcome was 6.5, with 91.7% sensitivity, 72.5% specificity, 27.0% PPV, 98.7% NPV, and 91.3% accuracy).[18]

Multiple bougienage may be required in 38.8%-57% of cases, based on a Nigerian[6] and Korean[14] studies. Successful permanent dilatation could be achieved in 14%-28.6% of cases.[6,7,14] No significant difference of wall circumference was found between dilatation-refractory stricture and dilatation-responsive stricture (72.50±27.87% vs 55.23±23.23%, p=0.098).[16]

In cases of dilatation failure, surgical therapies may be required, ranging from colonic interposition surgery,[6,13] jejunostomy,[7] or segmental resection and re-anastomoses, gastric tube interposition, or esophagocologastrostomy,[14] may be

required. In half of cases, supportive therapy was possible.[7] Morbidities found after colonic interposition surgery were cervical saliva fistula (18%), stenosis on anastomotic junction (6%), and obstruction, redundant colon accompanied with regurgitation, and poor intestinal function (3% each).[13] A cross-sectional study in Bahrain involving 46 strictures in pediatric patients showed no significant complications after dilatation sessions were found; thus, bougienage or balloon dilatation is generally considered safe for pediatric patients.[19]

A European prospective study involving 30 subjects in 3 groups was conducted to compare three types of stents for refractory benign esophageal stricture. Usage of polyester stent showed good outcome only on 10% of subjects, while 60% of subjects required further surgical treatment. Meanwhile, 30% success rate was achieved after biodegradable stent usage, and 60% requires dilatation or surgical treatment. Usage of metal stent was successful in 40% subjects, while 30% required re-stenting and 20% required dilatation. Similar outcome was seen on biodegradable (BD) or self-expandable metallic stent (SEMS) used, while self-expandable plastic stent (SEPS) was less successful.[20]

A retrospective cohort in Taiwan was conducted in 2020 and aimed to measure increased risk of esophageal carcinoma after caustic and pesticides ingestion, involving 21,840 subjects between 2000-2005 and followed-up to 2011. Esophageal carcinoma occurred in 1.66 per 10,000 person per year in control population. In pesticide ingestion group, involving organophosphates or carbamates, esophageal carcinoma occurred in 5.31 per 10,000 person per year (aHR: 2.52, 95% CI: 1.52-4.18; $p<0.05$). In caustic ingestion group, esophageal carcinoma occurred in 1.14 per 10,000 person per year (aHR: 0.98, 95% CI: 0.29-3.33; $p>0.05$); not significantly different than control population.[21]

Limitations of studies reviewed

All of studies mentioned had similar weaknesses. Most suffered from small sample size and differences in variables measured, making meaningful comparison and meta-analysis impossible to conduct. The studies were also only conducted in single center, and large-scale epidemiological studies were sorely lacking. Furthermore, country-wide studies should be conducted to assess true epidemiological extent of preventable, but highly morbid esophageal strictures after ingestions of caustic substances.

Majority of caustic ingestion and associated strictures involved pediatric population due to accidental ingestion. Alkali ingestions tend to cause more severe esophageal damage compared to acid ingestion. Radiological imaging, including CT scan and MRI, may help in determining damages involved. Degrees of damages are related with mortalities or morbidities, and dilatation may improve quality-of-life in some cases. In other cases, surgery may be required to improve quality-of-life. In pediatric patients, RDW, PEWS, and DROOL score may help in determining prognosis of patients.

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