Correlation of 99mTc Sucralfate Scan and Endoscopic Grading in Caustic Oesophageal Injury.
An Observational Analytic Study at Red Cross War Memorial Children's Hospital

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DECLARATION

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ABSTRACT

Background

Technecium (Tc) 99m Sucralfate scan has been shown to be a reliable and non-invasive screening modality after caustic substance ingestion, followed by oesophagoscopy under general anaesthesia to grade the extent and severity of injury [1]. However, the latter has associated morbidity [2], prolonged hospitalization and cost [3]. There is thus a need to delineate low grade caustic oesophageal injuries from high grade injuries by use of a non-invasive diagnostic modality.

Objective

To determine a correlation between the 99mTc Sucralfate scan and the endoscopy findings in children presenting with caustic oesophageal injury.

Methods

An observational analytic study of children who had both 99mTc Sucralfate scan and endoscopy after caustic substance ingestion at Red Cross War Memorial Children's Hospital (RCWMCH) in a period between January 2009 and September 2016. The oesophageal injury was classified into low grade and high grade according to the degree of adhesion on 99mTc Sucralfate scan and modification of Zargar endoscopic grading.

Results

Out of a total of 197 children, 40 children were identified who had both investigations done on average 26 (range, 1-55) hours post injury. Low grade adhesion on 99mTc Sucralfate scan was found in 27 children (68%), and all had low grade Zargar's oesophageal injuries. Household bleach ingestions belonged in this group. None of these subsequently developed residual pathology. Thirteen had high grade adhesion and five of these had high grade injury on endoscopy. Three (23%) developed oesophageal strictures. Correlation of 99mTc Sucralfate and endoscopic findings reached statistical significance with a p-value of 0.0014. No morbidity was associated with either the scan or endoscopy. Mean hospital stay in low grade oesophageal injuries was 1.55 (SD 0.83) days compared to 6.22 (SD 6.16) days in high grade injuries, *p*-value =0.003.

Conclusions:

We concluded that low grade sucralfate scan finding has potential to successfully eliminate the need for invasive endoscopy under general anaesthesia and thereby reducing procedure related morbidity, hospitalization and associated costs. However, mandatory endoscopy is required in children with high grade adhesion seen on 99mTc Sucralfate scan. This requires confirmation using a prospective study with larger number of cases.

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TABLE OF CONTENTS

CHAPTER 1

CHAPTER 1

PRE-AMBLE

South Africa is a middle-income country, divided in to nine provinces and each province allocated its annual budget to cover public sector health expenditure. Health care is delivered to 52 health districts through a complex network of primary, secondary and tertiary health care facilities.

According to a report on South Africa's children, their home and home environment produced by Statistics South Africa in 2013, there were about 5.8 million children aged 0-4 years in South Africa, representing 10.5% of the total population. With regard to health care, the overall majority of young children used public health care system (76.9%), whereas 16.1% used private sector providers and facilities [4, 5].

According to the 2010 data on mortality in children below the age of 5years, the most common specified non-natural cause of death was accidental poisoning and exposure to chemicals and noxious substances (0.9%) [4].

Background of Red Cross War Memorial Children's Hospital

Red Cross War Memorial Children's Hospital (RCWMCH) was established in 1956 and is the largest, standalone public tertiary hospital dedicated entirely to child health care in Southern Africa. The hospital is situated in Cape Town, Western Cape, South Africa. It is a world-renowned teaching hospital for the University of Cape Town committed to deliver world-class paediatric treatment, care, research and specialist training, with a full range of sub-specialities at quaternary, tertiary and secondary levels of care.

The RCWMCH manages around 260 000 children visits each year, of all races and socio-economic status below the age of 13 years, one third of which are younger than a year. Children from the Western Cape, the rest of South Africa and across broader Africa are referred by hospitals, clinics and smaller health care facilities.

One of the outstanding features of the hospital is having an onsite Poison Information Centre (PIC) that was established in 1971. This is one of only two national wide emergency poison call centers available 24 hours for both children and adult population. PIC uses telephone call and web based system which ensures an efficient and more accessible poisons advice service to medical professionals and the general public throughout Southern Africa. The internet based system, called Afritox, is accessible on- and off-line by medical professionals via the website https://www.afritox.co.za [6].

The majority of children exposed to poisonous substances are in fact managed as outpatients due to accessibility of the PIC and other web based search engines. Those who have ingested more potent agents; or live nearby the hospital; or have no access to internet or telephone calls seek medical help at the hospital trauma and medical emergency departments. From here they are either treated and discharged if the ingestion is deemed medically not harmful, or admitted to the trauma or surgical ward for Technecium (Tc) 99m Sucralfate scan [1] with or without endoscopy if a caustic injury is suspected. The availability of an efficient nuclear medicine department assists in detecting those with potential caustic injury to the oesophagus by use of 99mTc Sucralfate scan. Endoscopy is limited to those with positive 99mTc Sucralfate scan for further description of the oesophageal injury.

INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Caustic substance ingestion (CSI) is a tragic paediatric, surgical, and public health event – even in an era where there is legislation in place to prevent this. Children in the developing countries are commonly affected, especially those under six years of age [7-10].

Early recognition of caustic oesophageal injury (COI), and grading of the extent or severity thereof, will guide one towards appropriate management. Low grade oesophageal injury, once diagnosed, may require treatment with proton pump inhibitor, anti-fungal suspension and mucosal protective agent such as sucralfate. While in the majority of children the injured oesophagus heals without long term effects, and no further intervention is required, about 20% of children will develop significant oesophageal pathology [11]. High grade oesophageal injury may require much more extensive treatment, including the management described above, as well as a nasogastric tube to start early feeding and to maintain patency of the native oesophagus, careful follow up, and management of the injury sequelae.

The current protocol at Red Cross War Memorial Children's Hospital (RCWMCH) is to screen all children with the clinical suspicion of CSI by utilizing the 99mTc labelled Sucralfate scan. Those identified with an abnormal scan will receive a fibre optic endoscopy under general anaesthesia for grading of the extent and severity of injury, while those with normal scans will be discharged [12-14]. If a diagnosis of low grade injury could be established without endoscopy, it would circumvent the use of a general anaesthetic, the potential risk of endoscopy [13, 15], and decrease both hospitalization and cost [3].

The aim of this study was three-fold: to determine whether low grade and high grade oesophageal injuries can be identified clinically; the value of 99mTc Sucralfate scan in differentiating between low grade and high grade injury in comparison to fibre optic endoscopic findings; and the influence of these on subsequent management.

1.2 LITERATURE REVIEW

1.2.1 Methods

1.2.1.1 *Search Strategy*

A computerized search of the National Library of Medicine and the National Institutes of Health MEDLINE database was undertaken using the Entrez PubMed (www.pubmed.gov) interface. The primary search strategy was developed to retrieve English language articles focusing on caustic oesophageal injury. The systematic review search strategy is diagrammatically presented in table 1.

	Search Text	Citations
1	Oesophagus	88262
2	Caustic	12534
3	Caustic and Oesophagus	1255
4	Caustic and Oesophagus and Children	445
5	Caustic Oesophageal injury in Children	67

Table 1. Systematic Review Search Strategy

1.2.1.2 *Selection criteria*

Studies included in the systematic review pertaining to the diagnosis and management of caustic oesophageal injury in paediatric population were selected regardless of origin, hospital setting, or study design. In addition, animal studies related to the management were included.

1.2.2 Results

1.2.2.1 Articles for inclusion

Table 1 demonstrates the results of the systematic review. Using the search strategy as explained above in *1.2.1.1*, 67 titles and abstracts were found related to the diagnosis and management of caustic oesophageal injury. Three were rejected based on exclusion criteria. Eleven were excluded because they were not available in English. The remaining fifty three titles and abstracts were retrieved for full-text review. To these, twenty five were cross-referenced to ensure a thorough review. In total 78 articles were reviewed.

1.2.2.2 Qualitative Overview of Articles in Systematic Review

This systematic review was conducted in order to look at the available literature on caustic substance incidence; pathology and pathophysiology; clinical and imaging assessment; and particularly to answer the following questions as stated in the introduction:

1. To determine whether ‘low grade’ and ‘high grade’ oesophageal injuries can be identified clinically;
2. The value of 99mTc labelled Sucralfate scan in differentiating between low grade and high grade injury in comparison to fibre optic endoscopic findings,
3. The influence of these on subsequent management.

1.3 Caustic substances

Caustic substances are commonly used in households, industries and the agricultural environment (Table 2) [11]. Toddlers with their mobility and curiosity are often exposed to these substances, as it can be difficult to differentiate a caustic substance from common food items (Figure 1). Identifiable risk factors include low socio-economic status [16, 17] [18, 19]; male gender [20-22]; attention-deficit/ hyper-activity disorder symptoms [14]; poor parental supervision; poorly educated parents, and young maternal age [23-25]. A common scenario is that liquid caustic substances are decanted into either common cold drink bottles or smaller, clear, and unlabelled containers lacking childproof safety caps (usually 500ml bottles). The toddlers or even child minders confuse these bottles whilst searching for food or water to drink [26].

Caustic substance	Type	Commercially available form
Acids	Sulphuric	Batteries
		Industrial cleaning agents
		Metal plating
	Oxalic	Paint thinners, strippers
		Metal cleaners
	Hydrochloric	Solvents
		Metal cleaners
		Toilet & drain cleaners
		Antirust compounds
	Phosphoric	Toilet cleaners
Alkali	Sodium hydroxide	Drain cleaners
	Potassium hydroxide	Oven cleaners
		Washing powders
	Sodium carbonate	Soap manufacturing
		Fruit drying on farms
Ammonia	Commercial ammonia	Household cleaners
	Ammonium hydroxide	
Detergents, bleach	Sodium hypochlorite	Household bleach
	Sodium polyphosphate	Household cleaners
Condy's crystals	Potassium permanganate	Disinfectants, hair dyes

Table 2. Common caustic substances ingested [11]

Fig. 1 Common household items such as sugar, salt, corn flakes and spices can easily be confused with caustic soda (arrow) by children

Once ingested, the degree and extent of a corrosive injury depends on several factors which include: the nature of the caustic substance; its pH, concentration; the quantity swallowed; and the contact time with the tissues [10, 12, 14, 27, 28].

Strong alkalis, usually available in liquid and granular form, particularly crystalline grease cleaners (concentrated sodium hydroxide), are the principal causes of severe damage [16]. Household bleach, dishwasher detergents and other cleaning agents, all of which are mildly alkaline, are the most common caustic substances ingested. Household bleach showed no severe injuries in many studies [6, 21, 22, 29, 30]. Karaman et al. [21] evaluated 968 CSI with 460 bleach ingestions and none of them developed an oesophageal stricture. Ingestion of such caustic substances is usually limited to the oro-oesophageal mucosa and rarely causes injury to the submucosa or muscularis propria [31], which would result in stricture formation.

The physical form and the pH of the ingested caustic substance greatly affects both the site and type of oesophageal injury. The pH value more than 12 and less than 1.5 is associated with severe caustic injury [14, 32]. In general terms, the injury will vary according to whether the child swallowed the caustic substance in crystal, liquid or powder form. Crystalline drain cleaners (including concentrated sodium hydroxide) are strong alkalis and tend to become lodged in the proximal oesophagus. Highly concentrated caustic alkaline liquids usually pass quickly through the oropharynx and cause injuries to the upper, middle and lower oesophagus [16]. The powder form can also be inhaled and cause acute respiratory symptoms [14].

Many authors [10, 33-35] reported that the ingestion of alkaline substances is more prevalent than that of acid in corrosive oesophageal injuries. Thomas et al. [36], however, reported a contrary finding. Janseen et al. [3] found no significant difference in mucosal damage between the groups of caustic substances, although they found that alkaline substances were related to a longer hospital stay, and thus probably caused more severe injury.

1.3.1 *International and South African legislature on caustic substances*

Nearly all paediatric injuries are due to accidental ingestion that is potentially preventable [22] with 86–90% occurring within the home environment [23]. Due to the substantial morbidity and mortality associated with CSI, the international medical community demanded legislative action. In the USA, the Federal Caustic Act of 1927 was enacted through persistent efforts, requiring appropriate labelling of caustic substances, such as lye. Subsequently, the Poison Prevention Packaging Act of 1970 directed the US Consumer Product Safety Commission to require childproof containers and improved labelling of caustics and other potentially harmful household products [37, 38].

The South African government, through the Department of Labour, has gone into great lengths to instil adherence to the legislature on producing child-proof packaging, labelling, transportation and storage of caustic substances in accordance with SABS guidelines [Labour regulation 1179, Hazardous Chemical Substances Regulations, 1995] following the worldwide standards [37] . These legislative acts have somewhat decreased the incidence of CSI in high income areas. Low income areas [26] are, however, still affected by poor compliance mandating greater emphasis of such legislature especially in the latter group [39].

1.3.2 *Caustic substance ingestion incidence*

The true incidence of caustic substance ingestion is not known mainly because the majority of ingestions go unnoticed, are asymptomatic, or are unreported. The enactment of broad labelling and packaging legislation in Canada and in USA in the 1960s and 1970s resulted in decline of accidental child poisoning [40]. Comprehensive statistics collected in high income countries since the 1970s indicate a decrease in the incidence of severe CSI; however, many reports in the developing countries indicate persistence of this worldwide public health problem, as demonstrated by the need for oesophageal replacement procedures [39, 40].

The developing countries face many challenges, including lackadaisical data collection; insufficient or ineffective legal sanction application and societal non-adherence to caustic substance ingestion preventive legislation. Preventive medicine has not effectively reduced the incidence of such preventable accidents [16].

More than 200 000 incidences of caustic substance exposure were reported to the National Poison Data System of the United States in 2008 [16]. The incidence of caustic substance ingestion is reported at 5 to 518 paediatric caustic ingestion events per 100 000 population per year. Although noting a steady decline in higher income countries, low income countries are still highly affected [19, 41].

Poison Information Centre (PIC) statistics at RCWMCH in 2015 reported that 7 573 telephone calls relating to poisons were received by the PIC staff over the four-year study period and 3 896 were related to human poison exposures. Of these, 61.8% involved children <13 years; household bleach ingestion was the main exposure (73/142) [6].

1.4 *Anatomical pathology of caustic substance ingestion*

There is a fundamental difference in the injury sustained and region affected between the ingestion of alkaline and acid. Strong alkali substances immediately, within seconds, adhere and cause liquefactive necrosis of the affected area. The pathology is predominantly seen in the pharyngo-oesophageal region. The oral and pharyngeal burns are often seen, but they mostly heal with no pathological sequelae [29]. The oesophagus is the organ most commonly affected after CSI [12, 18, 42], and oesophageal injury will have a profound influence on the patient's ability to feed normally and to grow and develop. Such nutritional impairment can result in differential growth and poor quality of life. The site of oesophageal injury can be determined by the three anatomical zones of narrowing: the cricopharyngeal area; the middle oesophagus at the point of crossing of the aortic arch and the left main bronchus; and immediately above the oesophago-gastric junction [12, 42, 43].

Acid, on the other hand, causes coagulative necrosis on contact and rapidly glides down the oesophagus, usually without any serious damage. Acid substances have a pungent odour and taste sour. Children may therefore be reluctant to swallow more acid once tasted, resulting in less damage [12]. The pathological effect is usually seen in the antrum of the stomach. Acid ingestion results in pyloric spasm and subsequent pooling of acid at that site resulting in gastric outlet obstruction. The duodenum is usually protected from injury due to concomitant pyloric spasm [28, 44]. Clinically significant gastric injury is relatively uncommon in children. The severity of gastric injury is determined by the amount and pH of the caustic substance ingested and gastric contents at the time of ingestion [45, 46].

1.5 *Pathophysiology of caustic oesophageal injury*

The pathology of oesophageal injuries has been studied extensively using animal and human models [47]. Once the caustic substance has been ingested, there is a sequence of histo-pathological processes which will determine the pathology and subsequent management plan. The pathology is broadly divided into acute and late phases for description [36]:

Acute Phase

It is important to note that the acute inflammatory reaction is found in the acute phase irrespective of the causative agent. Ingestion of strong alkali induces liquefactive necrosis, which may involve the whole of the oesophageal wall, and even extends into the posterior mediastinum [12, 14, 48]. The destructive process continues until the alkali is neutralized.

In the first 24 hours after injury, haemorrhage, thrombosis of the submucosal vessels, and marked inflammation with oedema set in. Depending on the extent of injury, the inflammation may extend through the muscle layer until perforation occurs, with or without mediastinitis [36]. After 48 hours, submucosal vessels develop thromboses, triggering local necrosis and gangrene. Bacterial contamination (commonly 4-7 days post-injury) [14] leads to the development of small intramural abscesses, which may extend to the mediastinum in full-thickness injuries [10, 12]. Several days later, the necrotic tissue sloughs, the oedema is reduced, and neovascularization commences [14]. This early reparative (or subacute) phase, marked by weak tensile strength, develops from the end of the first week and throughout the second week after injury [12]. See Figure 2.

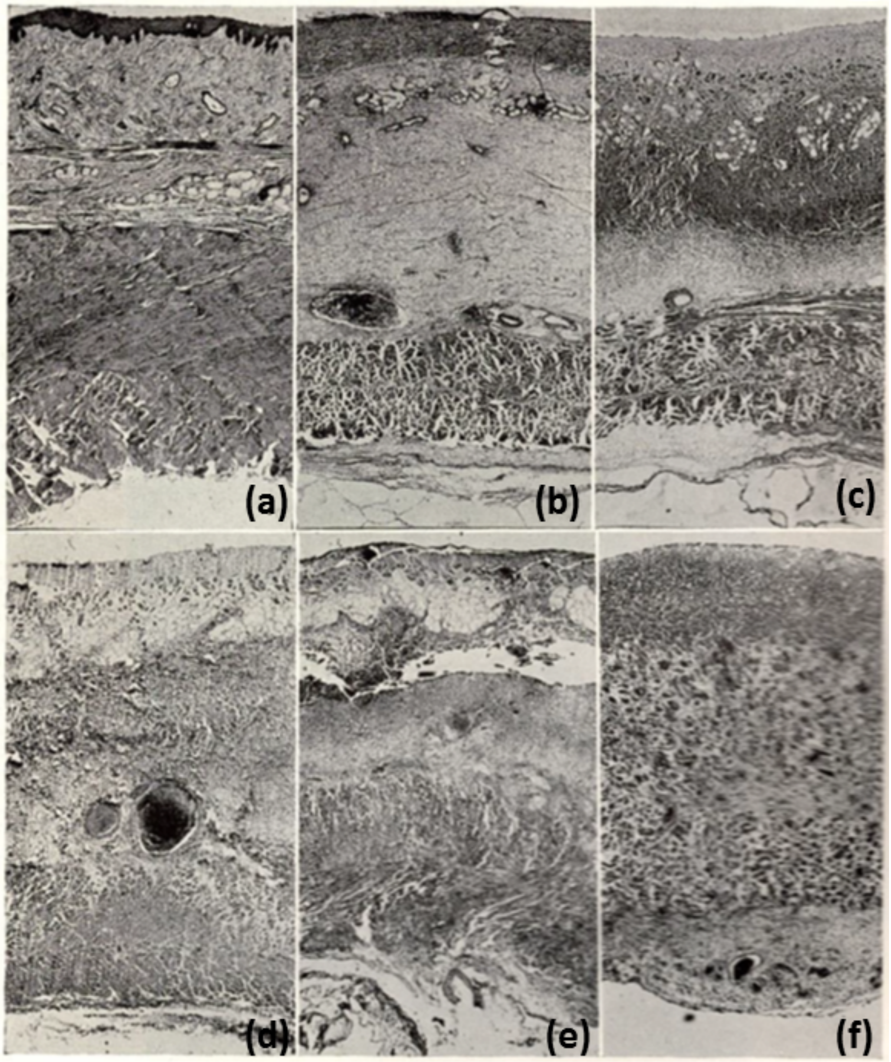

Fig 2. Histopathological changes demonstrating acute phase changes:

a) normal oesophagus. Note prominent muscularis mucosae and the relative thickness of various layers
b) 24hours post injury. Note absent epithelium, oedema and absence of cellular detail
c) 48 hours:inflammatory response in submucosa
d) thrombosed submucosal vessels and gangrene of superficial layers
e) liquifactive necrosis, intense inflammatory reaction and separation of superficial layer
f) 5 days: sloughed mucosa and submucosa, zone of inflammation and fibrin. Granulation tissue. Oedema and necrosis of muscular wall [47]

Late Phase

The late phase is characterized by the following pathological sequence. There is progressive cicatrisation of the affected oesophageal segment leading to stricture formation [36].

In the third week, the fibroblasts proliferate to replace the submucosa and the muscularis mucosa resulting in scar and stricture formation (Figure 3) [49]. This is followed by mucosal re-epithelialization, which is usually completed by the sixth week. Adhesions may form during this period, narrowing or obliterating the oesophageal lumen. The end result may be a fibrotic stricture and a shortened oesophagus (Figure 4), triggering gastro-oesophageal reflux (GOR) and motility disorder of the oesophagus [11, 22]. Oesophageal dysmotility may persist for several weeks, or may even become permanent if muscle is replaced by fibrous tissue. The injury may be so severe that trachea-oesophageal or even aorto-oesophageal fistulae may develop [11, 50].

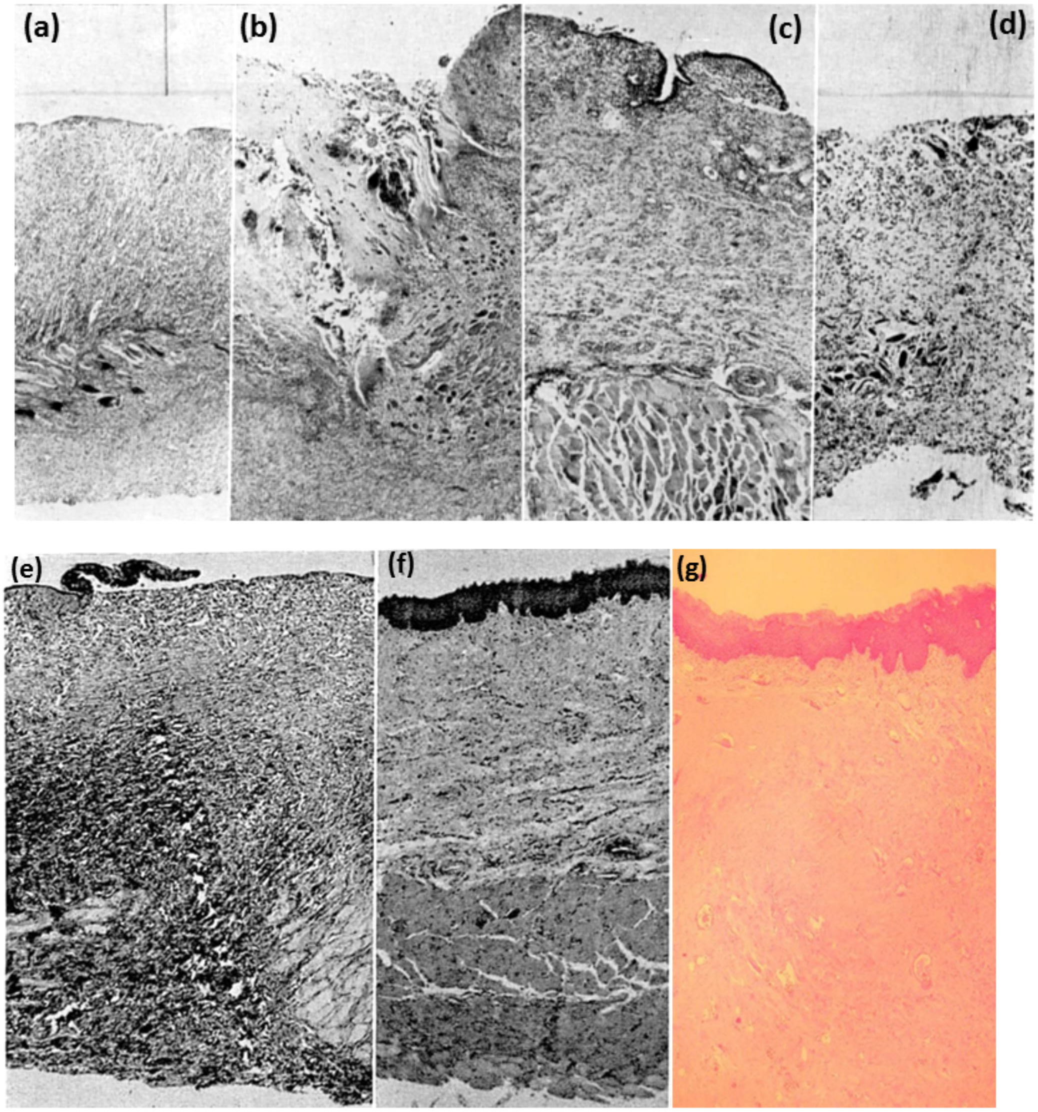

Fig. 3. Histopathological changes demonstrating late phase changes at 7days

a) organization and fibrosis,

b) intramural abscess, liquefaction and bacterial clumps,

c) epithelialization and progressive fibrosis;

d) 12days, complete necrosis of muscularis;

e) 4weeks, transmural fibrosis, regenerating epithelium covering granulation tissue;

f) 13weeks, epithelium covering a thick layer of fibrosis, and

g) 18weeks, regenerated epithelium and extensive fibrosis [47]

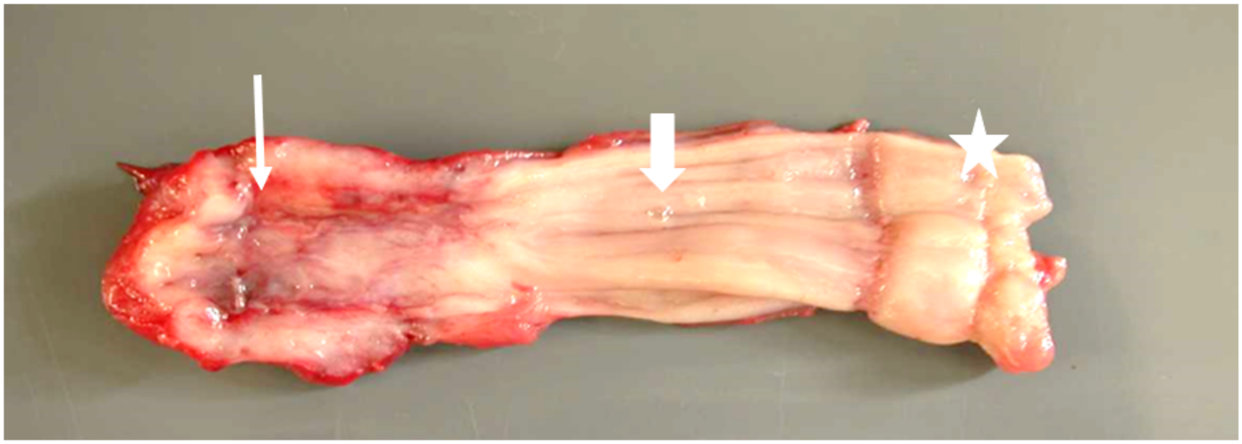

Fig. 4 Macroscopic image of an excised oesophagus 12 months post injury that resulted in oesophageal replacement. Proximal ulceration and structuring (narrow arrow) followed by an area of normal oesophageal mucosa (broad arrow) and the OG junction (star) is noted

1.6 *Diagnosis and Treatment of Caustic Oesophageal injury*

1.6.1 Clinical assessment

There is no clear consensus on the clinical assessment of caustic substance ingestion in the paediatric population. This might be partly due to the diversity of symptoms, which may vary from vomiting, drooling, intra-oral ulcers, dysphagia, refusal to feed, odynophagia, chest or abdominal pain, to respiratory symptoms. Drooling and dysphagia may indicate the presence of posterior pharyngeal or upper oesophageal injury [12] and children with these symptoms warrant further investigation.

The diagnosis of oesophageal injury is compounded by the fact that 57% of children are asymptomatic after reporting caustic ingestion [30]. Some authors [13, 21, 30, 51] regard the absence of symptoms as an indicator of minimal or no injury, obviating the need for diagnostic Endoscopy, although Temiz et al. [52] reported the presence of oesophageal lesions in 35% asymptomatic patients.

Gaudreault described how outcomes could be predicted based on initial symptoms/signs (S/S)

[53]. In this study, patients with a high degree of oesophageal injury or oesophageal stricture had a greater number of S/S, especially for those presenting with three or more S/S. Although there are studies showing increased likelihood of oesophageal injury with three or more symptoms [13, 18, 33, 53], some studies failed to show this correlation [14]. It is of concern that stricture formation has been reported in 1% of children with no oral signs of injury [21].

The pathology may not only be confined to the upper gastrointestinal tract. Airway injury occurs in 2-18% [14, 22] of caustic ingestions, caused by spillage of the caustic substance into the upper airway during ingestion or from vomiting. Inhaled concentrated caustic powder may cause nasopharyngeal oedema and lead to respiratory injury [12, 14, 22, 53].

Clinical symptoms and signs can be misleading, with delay in therapy resulting in a higher incidence of stricture formation [54]. Prompt diagnosis is therefore mandatory in all children with a history of CSI, irrespective of symptoms.

1.6.2 Pre-hospital first aid measures

The causative agent should be identified and immediately removed from the child. Induced vomiting should not be encouraged, as it can re-expose the oesophagus to the agent [21]. A neutral liquid such as water (pH 7) or milk (pH 6.5-6.7) may be considered to dilute and aid in neutralizing the agent [55]. Charcoal administration is not recommended as it does not absorb caustic agents and could interfere with the endoscopic evaluation [12]. A poison telephone help-line may assist in the identification of caustic contents and likely harm. Urgent medical attention should be sought [14].

1.6.3 Laboratory investigation

Laboratory confirmation with use of leucocyte count or C-reactive protein shows no useful predictive value in determining oesophageal injury or caustic stricture formation [33]. However, with oesophageal perforation, bio-chemical changes may be observed. The role of procalcitonin as a marker of ischemia has not been explored in this situation.

1.6.4 Imaging and endoscopy

Timely assessment of the severity of the CSI is important as it will determine future management [56].

The advent of 99mTc Sucralfate scan, an accurate and a non-invasive screening method by Millar et al. in 2001, changed the diagnostic algorithm [1]. Sucralfate is a sulphated disaccharide salt that forms stable complexes with proteins exposed in ulcerated mucosal surfaces by inhibiting their hydrolysis. Sucralfate can be labelled with technetium 99mTc to enable scintigraphy imaging [57]. It has become a reliable screening modality to identify injury to the oesophageal mucosa, and has a sensitivity of 100%, specificity of 81%, and negative predictive value of 100%. This method has become the preferred initial screening tool at RCWMCH.

In addition to the diagnostic advantages, performing a Sucralfate scan may also have therapeutic advantages. Sucralfate has an inhibitory effect on stricture formation by enhancing mucosal healing and suppressing stricture formation [58, 59]. The publication discussed above fell short in determining the pathological extent of injury to the oesophageal wall, and to date there are no studies indicating any correlation between the degree of sucralfate adhesion and the degree of oesophageal injury. As such, Sucralfate scanning currently remains a screening tool, and all patients with a positive scan are subjected to endoscopy. *The current study therefore, has been devised to address whether 99mTc Sucralfate scan be useful in differentiating those who will heal with minimal or no damage to the oesophagus in contrast to those who will develop significant pathological changes*.

Before the advent of 99mTc Sucralfate scan, upper GIT endoscopy was the standard initial diagnostic modality. Rigid oesophagoscopy may be dangerous in the early phase, hence flexible endoscopy has become the preferred endoscopic modality. This has now been surpassed by radioisotope scan as the initial screening modality followed by flexible endoscope to grade the degree and extent of oesophageal injury [12, 14].

Previous studies [43, 60, 61] arrived at different conclusions about the indications, timing and risks of esophagoscopy following ingestion of caustic substances. In 1999 Çiftçi [61] reported that the risk of perforation was theoretically much reduced after the introduction of fibre optic endoscopes. Endoscopy should ideally be performed within 24-48 hours [7, 12, 14, 51, 62, 63]. Endoscopy requires to be performed in a gentle manner, avoiding over-insufflation, under general anaesthesia in children to be safe. Even then, the endoscopy is an invasive method and general anaesthesia in children is associated with morbidity and mortality [2]. The risk of perforation increases beyond 48 hours due to acute necrotic phrase marked by friable mucosa [14]. Oesophageal injury can be graded on endoscopy as shown in Table 3 [13, 14, 51, 52, 64, 65].

Grade	0	I	IIa	IIb	IIIa	IIIb
Endoscopic necrosis appearance	No evidence	Mucosal	Superficial, non-circumferential	Deep or circumferential ulceration	Multiple scattered ulcerations	Extensive
Incidence	11-57%	11-18%	7-26%	13.6-27%	0.5-12%	0-1%
Risk of stricture	0%	0%	<5%	71.4%	~100%	

Table 3. Zargar grading of caustic oesophageal injury [14]

Because of the risk of perforation, oesophagoscopy should not be passed beyond a circumferential Grade IIb or III injury, thereby limiting its potential role [32, 66]. It is recommended that endoscopy should not be performed between 5 and 15 days post-injury due to the fragility of the oesophageal wall and the risk of perforation [14]. It is preferable to perform a contrast swallow between two [25] and three weeks [12, 14] post-injury to delineate the stricture. A contrast oesophagogram will show the number, length and calibre of the stricture(s) [36]. Once identified, regular oesophagoscopy and dilatation should be performed to restore the oesophageal lumen [12, 14, 25]. The Barium oesophagogram has a 30-60% false negative rate in the early diagnosis [66]. A strict follow-up in those who ingested acids has been recommended, due to delayed associated lesions [63].

Another promising screening method is the 99mTc Pyrophosphate scan, which experimentally showed a positive result on injured oesophageal mucosa in laboratory animals [4, 24]. The images correlated with histopathological findings, but this has not been validated in humans [24].

Endoscopic ultrasound reports in adults to determine the extent and depth of oesophageal injury concluded that the images can differentiate between oedema and deeper muscle injury that may have a higher risk of stricture formation [67]. These findings are contested [68] and risk of oesophageal perforation is unclear [14].

Computer Tomography scan (CT) or Magnetic Resonance Imaging (MRI) is occasionally needed where perforation or erosion into the adjacent mediastinal structures is suspected. CT scan offers a detailed evaluation of the oesophageal wall and surrounding tissues [12, 14]. However, accessibility and advocacy against radiation exposure in children limits its use in caustic ingestion [14]. MRI is recommended, when available.

1.6.5 Treatment overview

Grading the oesophageal injury provides valuable information regarding the immediate and future therapeutic approach (Figure 5) [69]. In rare circumstances, with a compromised laryngeal-pharyngeal injury, temporary endotracheal intubation may be required. Children with grade 0, I and IIa oesophageal injury are unlikely to develop complications, and are usually observed for 12-24 hours. Children with grade IIb and III oesophageal injuries should be observed whilst clear liquids, oral proton pump inhibitor, oral antifungal suspensions and sucralfate are given. During initial endoscopy a nasogastric tube is carefully passed to aid in feeding and to retain luminal patency that may be required in future prograde or retrograde dilatation of stricture(s).

A contrast swallow should be done two weeks after ingestion to delineate oesophageal damage [12, 14]. Gastrostomy may be required to maintain adequate nutritional status and to act as an avenue for retrograde string dilatation if required [34].

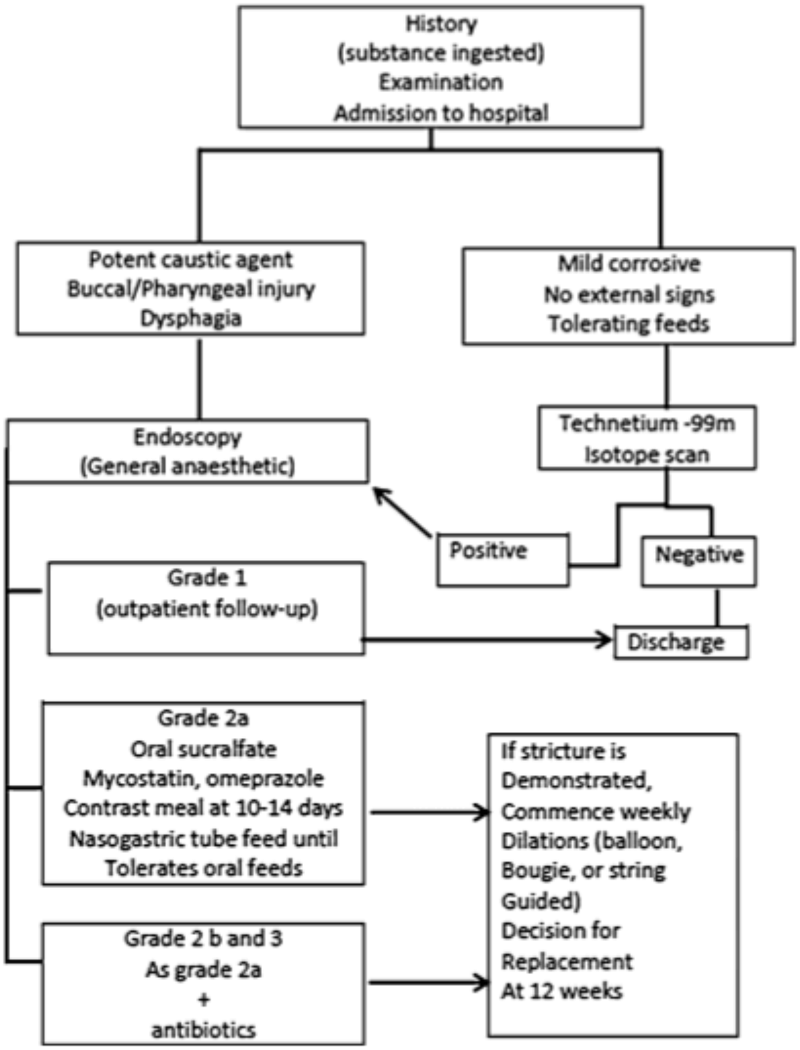

Fig. 5 Management protocol for caustic injuries of the oesophagus [11]

1.7 Sequelae of caustic oesophageal injury

The long-term sequelae of severe oesophageal injury is stricture formation. Unresolved strictures may lead to growth retardation, recurrent aspiration pneumonia, possible perforations, and a higher propensity to develop oesophageal malignancy. Panieri et al. [70] alluded to early factors predictive of failure of conservative treatment, which were: delay in presentation of more than one month; severe pharyngo- oesophageal burns requiring a tracheostomy; oesophageal perforation, inability to establish a lumen during the first session and a stricture longer than 5 cm on radiological assessment.

Strictures predominantly affect the proximal to mid-oesophagus, with rates that vary from 2% [29] to as high as 49% [11]. Early oesophagoscopy findings of a grade IIb or III injury; oesophageal stenosis on contrast oesophagogram; and persistent dysphagia at three weeks are of prognostic value to identify children who will require stricture dilation [14]. Serial stricture dilation is the mainstay of therapy for oesophageal strictures and oesophageal replacement is reserved for refractory strictures. Dilatation programs ideally start at three weeks post-injury [12, 14, 25, 34] and are repeated weekly or every second week, until the oesophagus has healed and an adequate luminal size is established.

Adjunct therapy to modulate scar formation includes the use topical or intra-lesion steroids or Mitomycin C. Use of steroids to prevent stricture formation after CSI is controversial. A meta-analysis of studies performed over 15 years concluded that steroids did not decrease the incidence of stricture formation [71, 72]. However, Hamza et al. [39], showed the beneficial effects of corticosteroids injections for localized strictures, with improvement and increase in dilatation intervals. Large scale randomized trials are needed to evaluate their risks and benefit.

Mitomycin C, the fibroblast-modulator, has been reported to be effective in resolving strictures with topical application via a rigid endoscope after dilation. A double-blind randomized study done on 40 paediatric cases showed lower dilatation requirements and higher resolution of strictures when used [73].

Other options are oesophageal stenting with nasogastric tube, silastic stents [64] or self-expanding covered metallic or plastic stents [74]. However, the stents are not universally available and would need to be manufactured in child sizes. They are difficult to remove. If there is no success in several months of dilatations, oesophageal replacement (Figure 4) is inevitable. Cakmak et al. reported a 5.7% incidence of oesophageal replacement in caustic strictures [20].

Unfortunately, oesophageal dilatation treatment or oesophageal replacement cannot prevent the development of oesophageal carcinoma in the retained oesophagus [25]. Oesophageal carcinoma is reported in 1-2% of patients after CSI [75-77]. Long-term surveillance for early detection of secondary oesophageal carcinoma is recommended from the second into the fifth decade after injury [77]. Gastric perforation is very rare. The gastric outlet obstruction may take up to three years to become clinically evident. Surgery may be necessary to bypass this obstruction [78].

1.8 Financial implications of routine sucralfate and endoscopy to diagnose caustic oesophageal injury

Sucralfate scan is a non-invasive investigative method with a100% sensitivity. It can be done on an outpatient basis, without hospitalization, and does not require an anaesthetic. In comparison oesophagoscopy needs hospitalization and general anaesthesia, and carries a possibility of oesophageal damage. Both these investigatory methods are complementary to one another. A negative sucralfate scan can exclude between 50% [1] and 61% [3] of children that would have had endoscopy following caustic ingestion. A positive Sucralfate scan, will in the current protocol at RCWMCH, however, lead to endoscopy with added cost and risk of complications.

Janseen et al. [3] in 2015 reported on the significant cost difference between performing a 99mTc Sucralfate scan and endoscopy, estimated at R1 285.00 and R4 867.00 per child respectively. Therefore, the cost saving of performing a 99mTc Sucralfate scan without performing a subsequent endoscopy can save about R3 582.00 per patient (this is a 74% difference in cost). In 143 children with caustic ingestion who had a negative 99mTc Sucralfate scan, not performing a subsequent endoscopy resulted in an estimated cost saving of 143 x R3 582.00 totalling R512 226.00. These costs did not include additional costs, such as professional fees, which a patient pays at a private hospital. The total costs saved by performing a sucralfate scan as primary diagnostic procedure instead of performing an endoscopy were R446 964.00 (approximately 40 000 USD) in 234 patients.

1.9 Summary of literature review

Caustic oesophageal injury is common in young children and can have significant long-term sequelae if not correctly diagnosed and managed. Symptoms cannot accurately diagnose the presence and extent of injury. Hence, the need for special investigations. Two methods are used to identify the presence and extent of potential injury, namely, the 99mTc Sucralfate scan and upper gastrointestinal endoscopy. The 99mTc Sucralfate scan differentiates between no injury and injury to the oesophagus. With a positive isotope scan endoscopy is required to grade the extent and severity of the injury and to determine further management.

1.10 Aims

Three questions remain however, namely:

1) can low grade and high grade oesophageal injuries be identified clinically
2) does the 99mTc Sucralfate scan correlate with endoscopic grading to differentiate between low grade and high grade injury
3) the influence of the two modalities on further management

An observational analytic study was undertaken to answer these three fundamental questions.

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CHAPTER 2

PUBLICATION-READY MANUSCRIPT

2.1 Title page

2.1.1 Title of paper

"CORRELATION OF 99mTc SUCRALFATE SCAN AND ENDOSCOPIC GRADING IN CAUSTIC OESOPHAGEAL INJURY"

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2.1.3 *Supplementary information*

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Reprints: No reprints

Keywords: paediatric; caustic substance ingestion; oesophageal injury; diagnosis; 99mTc Sucralfate scan

2.2 Mini abstract

Caustic oesophageal injuries have a variable presentation. Severe injuries commonly heal by stricture formation, however the "low grade" injuries do not. We demonstrate the possibility to predict the "low grade" caustic oesophageal injury on 99mTc Sucralfate scan, thereby, reducing hospital stay, cost and morbidity related to general anaesthesia and endoscopy.

2.3 Structured abstract

Background

Technecium (Tc) 99m Sucralfate scan has been shown to be a reliable and non-invasive screening modality after caustic substance ingestion, followed by oesophagoscopy under general anaesthesia to grade the extent and severity of injury [1]. However, the latter has associated morbidity [2], prolonged hospitalization and cost [3]. There is thus a need to delineate low grade caustic oesophageal injuries from high grade injuries by use of a non-invasive diagnostic modality.

Objective

To determine a correlation between the 99mTc Sucralfate scan and the endoscopy findings in children presenting with caustic oesophageal injury.

Methods

An observational analytic study of children who had both 99mTc Sucralfate scan and endoscopy after caustic substance ingestion at Red Cross War Memorial Children's Hospital (RCWMCH) in a period between January 2009 and September 2016. The oesophageal injury was classified into low grade and high grade according to the degree of adhesion on 99mTc Sucralfate scan and modification of Zargar endoscopic grading.

Results

Out of a total of 197 children, 40 children were identified who had both investigations done on average 26 (range, 1-55) hours post injury. Low grade adhesion on 99mTc Sucralfate scan was found in 27 children (68%), and all had low grade Zargar's oesophageal injuries. Household bleach ingestions belonged in this group. None of these subsequently developed residual pathology. Thirteen had high grade adhesion and five of these had high grade injury on endoscopy. Three (23%) developed oesophageal strictures. Correlation of 99mTc Sucralfate and endoscopic findings reached statistical significance with a p-value of 0.0014. No morbidity was associated with either the scan or endoscopy. Mean hospital stay in low grade oesophageal injuries was 1.55 (SD 0.83) days compared to 6.22 (SD 6.16) days in high grade injuries, *p*-value =0.003.

Conclusions:

We concluded that low grade sucralfate scan finding has potential to successfully eliminate the need for invasive endoscopy under general anaesthesia and thereby reducing procedure related morbidity, hospitalization and associated costs. However, mandatory endoscopy is required in children with high grade adhesion seen on 99mTc Sucralfate scan. This requires confirmation using a prospective study with larger number of cases.

2.4 Main Paper

Introduction

The ingestion of caustic substances by children is a major cause of morbidity and mortality, especially in the low and middle-income countries [4-6]. Children under the age of six years are most at risk due to the lack of an enabling nurturing environment; lack of supervision [7-9]; inappropriate storage [4]; and use of many of these hazardous substances within households [9-12]. The offending agents are mostly strong alkali and acids, with oxidizing substances such as household bleach being common [13, 14]. Consequences are significant, as up to 20% of children could develop significant oesophageal damage resulting in stricture formation [15].

Early recognition of caustic oesophageal injury and grading of the extent or severity thereof, will guide towards appropriate management [16]. Traditionally, the presence and extent of oesophageal injury was determined by clinical symptomatology, radiology, and endoscopy under general anaesthetic [14, 16-19]. In 2001, the 99mTc Sucralfate scan was introduced as a non-invasive method to determine whether the oesophagus was injured by caustic ingestion [1]. This investigation has a negative predictive value of 100% and has been shown to be cost-effective.

The current protocol at Red Cross War Memorial Children's Hospital (RCWMCH) is to screen all children with the clinical suspicion of CSI by utilizing the 99mTc Sucralfate scan. Those identified with an abnormal scan will receive a fibre optic endoscopy under general anaesthesia for grading of extent and severity of injury, while those with a normal scan are discharged [1, 3]. This practice has excluded between 50% and 61% of children who have swallowed caustic substances from endoscopy [1, 3]. There is, however, a subgroup of children on Sucralfate scan that have been identified to have 'low grade' or minor sucralfate adherence. The significance of this finding has not been determined. It would be of great benefit, if a subgroup of children can be identified on isotope scan that would require no further investigation or treatment.

The aim of this study was three-fold: to determine whether low grade and high grade oesophageal injuries can be identified clinically; the value of 99mTc Sucralfate scan in differentiating between 'low grade'/ minor and 'high grade'/ severe injury in comparison to fibre optic endoscopic findings, and thirdly, the influence of these on subsequent management. If a diagnosis of low grade injury can be established without endoscopy, it will circumvent general anaesthesia, the potential risk of endoscopy [20], decrease hospitalization and cost [3].

Material and Methods

This was an observational analytic study aimed at reviewing the records of all the children who had 99mTc Sucralfate scan and endoscopy after caustic substance ingestion at RCWMCH in a period between January 2009 and September 2016. The case records were obtained from the surgical and nuclear medicine database, and the following information was extracted: patient demographics; clinical presentation; sucralfate scan and endoscopy findings; length of hospital stay; postoperative complications; and follow-up. The caustic substances were identified by common name as described by the parent or caregiver. Study subjects included all children who have had both, 99mTc Sucralfate scan and endoscopy. Children were excluded from the review if they had only one of the methods of investigation. The standard protocol was used to investigate and manage children with suspected caustic substance ingestion (Figure 1).

The 99m Tc sucralfate mixture was prepared in-house using the method described by Crama-Bohbouth et al. [21]. The dose was calculated using the 99m Tc Colloid (gastric reflux) recommended dose on the EANM dosage card [22]. The 99mTc sucralfate was given orally followed by 20 ml milk which was used to wash off excess sucralfate from the oesophagus.

For the studies recorded from 1 January 2009 until the first of September 2015 the children were imaged on a Philips Axis Dual Head camera. From the first of 1st September until end September 2016 the children were imaged on a GE Discovery NM/CT 670 Pro camera (GE healthcare, Chicago, Illinois, USA). All children were imaged supine using LEHR collimators. An initial dynamic sequence was recorded at a frame rate of 0.5 seconds per frame for 1 minute using a 128 x 128 matrix. This was followed by a posterior static image with a 256 x 256 matrix, recorded for 300 seconds.

The images were inspected visually and if no activity was seen in the expected position of the oesophagus it was classified as normal. If faint activity was seen in the expected position of the oesophagus it was classified as low grade adhesion of sucralfate. If the activity was clearly visualised it was classified as high grade adhesion of sucralfate (Figure 2). Buccal and gastric activity was excluded from analysis.

For all children with a positive 99mTc Sucralfate scan result, gentle fibre optic endoscopy was performed under general anaesthesia. Oesophageal injury was classified according to the Zargar grading system, which was subsequently modified to differentiate between low grade and high grade injuries as determined by the prevalence of developing oesophageal stricture. (Table 1).

Approval of the study by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee was obtained, REF. 049/2017. The Red Cross War Memorial Children's Hospital scientific committee granted permission for the study.

Statistical methods

The data was collected and analysed with the use of Microsoft access and Excel spreadsheet. Data analysis was done through the departmental statistician. Continuous variables were compared with the use of the *t* test, Kruskal-Wallis test. Chi-square analysis and the Fisher exact test were used for the analysis of the categorical variables where appropriate. *P* values of less than 0.05 were considered significant. Statistical calculations were done using R version 3.3.2 (2016-10-31) – "Sincere Pumpkin Patch" Copyright (C) 2016 The R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64 (64-bit).

Results

A total of 197 children ingested a caustic substance and all had a 99mTc Sucralfate scan. Seventy-three children were potentially eligible for the study, of whom 29 had incomplete clinical data, and four either had delayed or no endoscopy. Forty children satisfied the inclusion criteria of having had both investigations done on average 26 (range, 1-55) hours post injury. There were 21 males and 19 females, with a mean age of 33.25 (range, 6-134, SD 25.38) months at presentation.

The caustic substances, pH, 99mTc Sucralfate and endoscopic findings and sequelae are depicted in Table 2. The majority of ingested caustic substances, eleven (27.5%), were the oxidizing/reducing agent in the form of household bleach, and all these had low grade oesophageal injury on both, 99mTc Sucralfate scan and endoscopic findings. None of them subsequently developed oesophageal strictures. The second most common caustic substances ingested were strong alkaline in either liquid, crystal or powder form, with pH varying from 9-13. Liquid alkaline ingestions caused the most severe injury with three developing oesophageal strictures. Acid ingestion was infrequently seen in three children (7.5%) and none of these developed long-term oesophageal injury.

Ten children (25%) received first aid at home to counteract the effect of the ingested agent, namely milk (n=6); activated charcoal (n=2); water and honey in one each. All of these children, except one had low grade injury.

The symptoms experienced by 40 children after caustic substance ingestion varied considerably. All children were symptomatic, with the four main symptoms and signs: vomiting, drooling, dysphagia and buccal mucosa lesions. Vomiting was a presenting complaint in 22 (55%) of which one developed oesophageal stricture. Drooling and dysphagia was noted in 10 (25%), of which two had high grade oesophageal injury resulting in oesophageal stricture. Six (15%) children presented with buccal mucosa injuries and had low grade oesophageal injuries. High grade oesophageal injury resulting in stricture was associated with the combination of drooling and buccal mucosa injury in four children. Household bleach ingestions were characterized by vomiting. None of these presented with drooling or buccal mucosa ulcers.

All children had 99mTc Sucralfate scan within 12-24 hours of sustaining the injury and the findings were: 27 low grade (67.5%) and 13 high grade (32.5%).

The time lapse between the estimated time of caustic substance ingestion and endoscopy for those with low grade adhesion was a mean of 26.42 (range, 1-55, SD 13.65) hours as compared to high grade adhesion with mean of 24.57 (range of 6-35, SD 9.43) hours, p=0.82. The endoscopic grading identified 35 low grade and 5 high grade injuries. Of the latter three developed strictures.

All 27 (67.5%) children diagnosed with low grade adhesion on 99mTc Sucralfate scan were found to have Grade 0, I and IIa on endoscopic oesophageal injury grading. All were discharged home on day two, on oral feeds and proton pump inhibitor. In addition, none with the low grade adhesion on 99mTc Sucralfate scan demonstrated high grade oesophageal injury (Grade IIb, IIIa or IIIb) on endoscopic grading. The correlation between the two investigation modalities is statistically significant, with *p* value=0.0014 (Table 3).

High grade adhesion as diagnosed on 99mTc Sucralfate scan was seen in 13 children (32.5%), eight had low grade oesophageal injury on endoscopic grading (Grade 0, I and IIa) and five had high grade (Grade IIb and IIIa) on endoscopic grading of oesophageal injuries. Three children of the latter group developed oesophageal strictures, of whom one needed oesophageal replacement and the others were successfully dilated (Table 4).

The length of hospital stay was directly proportional to the severity of the oesophageal injury. Low grade injuries stayed on average 1.55 (range, 1-4) days and high grade injuries 6.22 (range, 1-18) days. This was statistically significant, with *p=0.003*

There was no mortality related to either the disease or the investigations performed in this study. No gastrointestinal or respiratory morbidity was documented in children with low grade oesophageal injuries. Three of five children with high grade oesophageal injuries on both the 99mTc Sucralfate scan and endoscopy developed oesophageal strictures. The causative agent, pH value, scan and endoscopic grading of three children is depicted in Table 4. Their corresponding sucralfate scans and contrast images are depicted in Figures 3, 4 and 5 illustrating the value of the initial scan related to the subsequent outcome.

Discussion

The current literature indicates that drooling, intra-oral mucosal injury and dysphagia may indicate significant oesophageal pathology [5, 23]. In our study, this combination of symptoms was present in 35% of whom 14% developed oesophageal strictures. Therefore, children with these symptoms should be investigated [13, 17]. This study has also identified other factors that could be used for risk stratification of diagnosing significant oesophageal injury, which would require further therapeutic intervention, namely: the ingestion of strong liquid alkaline agent; high grade adhesion on 99mTc Sucralfate scan, and Grade IIb and III on endoscopic grading.

With respect to the second aim, our results confirmed the possibility of differentiating between children with low grade and high grade caustic oesophageal injury, as diagnosed on 99mTc Sucralfate scan and confirmed on endoscopy. None of the children with low grade oesophageal injury or those who ingested household bleach, a common aetiological factor, later developed significant oesophageal injury requiring intervention. This study thus suggests that a more goal-directed approach should be utilized in the initial investigation of caustic substance ingestion (CSI).

In a four-year retrospective cross-sectional study on human poison exposure-related telephone calls to RCWMCH Poison Information Centre, 3 896 telephone calls were made relating to human poison exposures. Of these, 61.8% involved children <13 years and 46.9% were referred for endoscopy [24]. Due mostly to legislation, the incidence of caustic substance ingestion has diminished to approximately 5 to 518 paediatric caustic ingestion events per 100 000 population per year, although low income countries still carry a major disease burden [6]. As many of these affected children would require endoscopy for diagnosis, there is a definite need to identify children with minor injury that would require no further intervention from those that would require investigations and follow-up.

The pathology of oesophageal injuries has been studied extensively using animal and human models [25]. Once the caustic substance has been ingested there is a sequence of histo-pathological processes which will determine the pathology and subsequent management plan.

Not all ingested caustic substances will result in significant oesophageal injury. The injury is related to the offending caustic substance pH value, its concentration, and contact time [5, 8, 17, 25]. Oxidising substances, such as household bleach, are the most common ingested agents, although they rarely cause significant long-term sequelae [13, 26]. Two studies have reported findings contrary to this, although one author was not certain about the concentration of the caustic substances [8, 27]. The majority of ingested caustic substances in our study were oxidizing/reducing agent in the form of household bleach (n=11). The study identified that if a child has a history of household bleach ingestion, further investigations are unwarranted, as all children had low grade injury on both scan and endoscopy, with no long-term consequences. A large retrospective study of 968 paediatric CSI by Karaman et al. in 2015 [13] demonstrated no stricture formation or complication following 460 household bleach ingestions.

Strong alkalis caused the most severe injuries, as reported by many and have the most devastating sequel on the oesophagus [9, 28-30]. The pH of the caustic substances varied from 9-13 in our series, resulting in high grade adhesion on 99mTc Sucralfate scan and endoscopic findings of Grade IIb and IIIa, with an overall risk of developing an oesophageal stricture of 7.5% and oesophageal replacement of 2.5%. The risk of developing an oesophageal stricture, however increased exponentially with high grade adhesion to 23%. This is comparable to other studies where the need for oesophageal replacement is 2 –49% [8, 15, 26].

Ingestion of acid is uncommon in Africa, which is supported by our findings, although a meta-analysis reported a risk as high as 30.7% [14]. High grade oesophageal injury may require much more extensive treatment, including a nasogastric tube to start early feeding and to maintain patency of the injured oesophagus, careful follow up and management of the sequelae.

Traditionally, the diagnosis of caustic oesophageal injury included contrast oesophagogram and flexible endoscopy. The contrast oesophagogram has a 30-60% false negative rate in the early diagnosis [31]. Rigid oesophagoscopy may be dangerous in the early phase, hence flexible endoscopy has become the preferred endoscopic modality. However, because of the risk of perforation, it should not be passed beyond a circumferential Grade IIb or III injury, thereby limiting its potential role [31, 32].

The advantages of 99mTc Sucralfate scan, as an initial investigation is that it is in a liquid form and therefore, can visualize the entire length of the oesophagus [5, 10, 14, 17, 19, 23]. Sucralfate, sucrose octosulfate complex, is a tissue protective agent that forms a physical barrier between the damaged gastrointestinal mucosa and causative agent. It forms stable complexes with proteins exposed in ulcerated mucosal surfaces, with an affinity of six to seven times higher than to normal mucosa, by inhibiting their hydrolysis [33, 34]. Sucralfate can be labelled with technetium 99mTc to enable scintigraphy imaging [1, 34].

Our current protocol is to perform the radioisotope study ab-initio in all children with suspected CSI, irrespective of symptoms, followed by endoscopy within 24-48 hours of caustic ingestion if the scan is positive. Previous studies from our institution have shown that 99mTc Sucralfate scan is a safe, cost-effective and reliable screening modality to detect oesophageal injury, with a sensitivity and negative predictive value of 100% [1, 3], hence, those with a negative sucralfate scan are no longer subjected to endoscopy. In a meta-analysis in 2016 of caustic ingestion in 8 388 children, endoscopy was the standard investigatory method in nearly all the children [14]. The authors would propose that the scan should become the initial investigation method for all children post caustic exposure in centres where nuclear medicine departments exist, as it could avoid invasive endoscopy and general anaesthetics in 50-61% of children [1, 3].

In addition to the diagnostic advantages, performing a sucralfate scan may also have therapeutic advantages. It has an inhibitory effect on stricture formation by enhancing mucosal healing and suppressing stricture formation [34]. In an adult study, the frequent use of sucralfate over a period of time has reduced stricture in Grade IIb and III injuries from 87 to 12.5% [33]. With a positive scan, endoscopy should ideally be performed within 24-48 hours followed by flexible endoscope to grade the degree and extent of oesophageal injury [5, 34]. No systemic adverse reactions were associated with sucralfate [33].

From a practical point of view, the 99mTc Sucralfate scans were divided into low grade and high grade to differentiate the injuries that heal without consequences and those that were potentially more severe. Sucralfate scan can identify microscopic injury in comparison to endoscopy that may not be able to detect these subtle microscopic changes [3]. All those children with low grade adhesion had corresponding oesophageal Grade 0, I and IIa. All healed with no pathological sequelae. However, even with low grade adhesion, none of the endoscopic findings was more extensive than superficial, non-circumferential injury. In contrast, 13 of 99m Tc Sucralfate scan adhesions were identified as high grade. On endoscopy, eight of these showed superficial mucosal damage (Grade ≤ IIa, and five showed high grade injury. Of these, three developed oesophageal strictures. Although, the 99mTc Sucralfate scan overestimated the degree of oesophageal damage by 62%, the fact remains that, 23% had significant oesophageal damage resulting in stricture formation. Therefore, all children with high grade adhesion on radioisotope scan must undergo endoscopy to determine the extent and severity of oesophageal injury.

With this method, we can now confidently differentiate between minor oesophageal injury requiring no further management from those that would require endoscopy and further management. Therefore, a low grade positive Sucralfate scan is not *sine qua non* for endoscopy.

This study had some limitations inherent to its retrospective nature – especially as relates to missing or incomplete patient records. The 99mTc Sucralfate scan can only be used to assess oesophageal injury, and not concomitant intra-oral or gastric pathology. It is assumed that those with low grade injuries suffered no further consequences as none returned for follow up, although our patient study is small. The noted shortfall in this study was reporting the uptake of Sucralfate on the injured oesophagus based on visual inspection and lack of quantifiable parameters. A larger, prospective study would be necessary to unequivocally answer this clinically important question and further define the 99mTc Sucralfate scan analysis and reporting method. Although a detailed cost evaluation of performing these investigations was not part of the protocol, we have determined that the mean hospital stay in low grade oesophageal injuries was 1.55 (SD 0.83) days compared to 6.22 (SD 6.16) days in high grade injuries, p-value =0.003, this in itself contributed to a significant cost reduction.

Conclusion

Drooling, intra-oral mucosal injury, dysphagia and the ingestion of strong liquid alkaline agent may indicate significant oesophageal pathology and further investigation is warranted in these patients. Sucralfate scans offer useful information in all children with caustic ingestion. This study has confirmed that endoscopy is not needed when household bleach has been ingested. Low grade adhesion on 99mTc Sucralfate scan requires no endoscopy or further management, obviating the use of invasive endoscopy under general anaesthesia and reducing procedure related morbidity, hospitalization and associated costs. We would suggest mandatory endoscopy in children with high grade adhesion on 99mTc Sucralfate scan. We have identified a trend which may have significant implications, however the population size is small and an expanded prospective study is warranted to confirm these findings.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
For this type of study formal consent is not required.

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2.6 Captions

Tables

Table 1. Modified Zargar endoscopic grading of caustic oesophageal injury dividing the endoscopic grading into low grade and high grade as determined by the risk of stricture formation [14]

Table 2. Caustic substances form, pH, 99mTc labelled sucralfate scan, endoscopic findings and complications

Table 3. Sucralfate by endoscopic findings. Sucralfate, p-value generated using fishers exact test.

Table 4. Correlation of Caustic agents' pH, 99mTc labelled Sucralfate scan, endoscopic grading and stricture formation

Figures

Fig. 1 Management protocol for caustic injuries of the oesophagus [11]

Fig. 2 99mTc Sucralfate scan showing, a) normal oesophagus with no sucralfate adhesion; b) low grade (faint) adhesion on the distal ½ of the oesophagus, and c) high grade adhesion of sucralfate on the oesophagus

Fig. 3 Case 1. a) 99mTc Sucralfate scan showing high grade Sucralfate adhesion on the distal 1/3 of the oesophagus. Contrast swallow demonstrates b) mid–lower oesophageal stricture 3weeks post CSI

Fig. 4 Case 2. 99mTc Sucralfate scan shows high grade adhesion of Sucralfate to the entire oesophagus. Contrast swallow demonstrates: a) long caustic oesophageal stricture with prestenotic dilatation, and b) normal oesophageal caliber post oesophageal dilatation program

Fig. 5 Case 3: Sucralfate scan and contrast swallows: a) 99mTc Sucralfate scan showing high grade Sucralfate adhesion on the entire oesophagus; b) Contrast swallow demonstrates subtle mid oesophageal narrowing with mild mucosal irregularity extending from T4-T8, and c) colonic oesophageal replacement

2.7 Supplementary file

2.7.1 <u>**Tables**</u>

Zargar's Grade	**0**	**I**	**IIa**	**IIb**	**IIIa**	**IIIb**
Endoscopic appearance	No evidence Of injury	Mucosal erythema and oedema	Superficial non-circumferential erosion, ulcers, haemorrhage or exudate	Deep or Circumferential ulceration	Multiple scattered ulcerations, patchy necrosis (brown, black or grey)	Extensive necrosis
Incidence	11-57%	11-18%	7-26%	13.6-28%	0.5-12%	0-1%
Risk of stricture	0%	0%	<5%	71.4%	~100%	
Modified Grade	LOW GRADE			HIGH GRADE		

Table 1. Modified Zargar endoscopic grading of caustic oesophageal injury dividing the endoscopic grading into low grade and high grade as determined by the risk of stricture formation [14]

Form of Caustic substance	pH	No.	99mTc labelled Sucralfate scan (n)	Endoscopic findings	Sequelae
Bleach	12.6	11	Low grade =11	Grade 0 =7 Grade 1 =2 Grade 2a =2	Nil
Liquid Alkaline: oven cleaner =4 drain cleaner =1 cleaning solutions = 6 other =3	9-14	14	Low grade =7 High grade =7	Grade 0 =5 Grade 1 =3 Grade 2a =2 Grade 2b =2 Grade 3a =2	Oesophageal strictures developed in 3 with Grade 2b & 3a
Crystal Alkaline: K permanganate =3 caustic soda =5	13	8	Low grade =4 High grade =4	Grade 0 =4 Grade 1 =2 Grade 2a =2	Nil
Powder Alkaline: caustic soda =2	13	2	Low grade =1 High grade =1	Grade 2a =1 Grade 2b =1	Nil
Acids =3	1-3	3	Low grade =2 High Grade =1	Grade 1 =3	Nil
Hair relaxer =2	9-13	2	Low grade =1 High grade =1	Grade 0 =2	Nil
Total		40			

Table 2. Caustic substances form, pH, 99mTc labelled sucralfate scan, endoscopic findings and complications

Variable	Levels	Grade 0: number (%)	Grade I: number (%)	Grade IIa: number (%)	Grade IIb: number (%)	Grade IIIa: number (%)	All: number (%)
Sucralfate	High grade	3 (15.8)	1 (11.1)	4 (57.1)	3 (100)	2 (100)	13 (32.5)
	Low grade	16 (84.2)	8 (88.9)	3 (42.9)	0 (0.0)	0 (0.0)	27 (67.5)
P=0.0014	all	19 (100.0)	9 (100.0)	7 (100.0)	3 (100.0)	2 (100.0)	40 (100.0)

Table 3. Sucralfate by endoscopic findings. Sucralfate, p-value generated using fishers exact test.

Caustic agent	Ph	99mTc Sucralfate scan	Endoscopic grading	Sequelae
Cleaning solution (case 1, Fig. 3)	11-13	High grade- entire oesophagus	Grade 3a-entire oesophagus	Long oesophageal stricture prox-lower
Oven cleaner (case 2, Fig. 4)	13	High grade-distal 1/3 oesophagus	Grade 2b-mid lower oesophagus	Middle-lower oesophageal stricture
Stain remover (case 3, Fig. 5)	9-10	High grade -entire oesophagus	Grade 2b prox 1/3 oesophagus, Grade 3a dist 2/3 oesophagus	Middle (t4-t8) oesophageal stricture -> oesophageal replacement

Table 4. Correlation of Caustic agents' pH, 99mTc Sucralfate scan, endoscopic grading and stricture formation

2.7.2 **Figures**

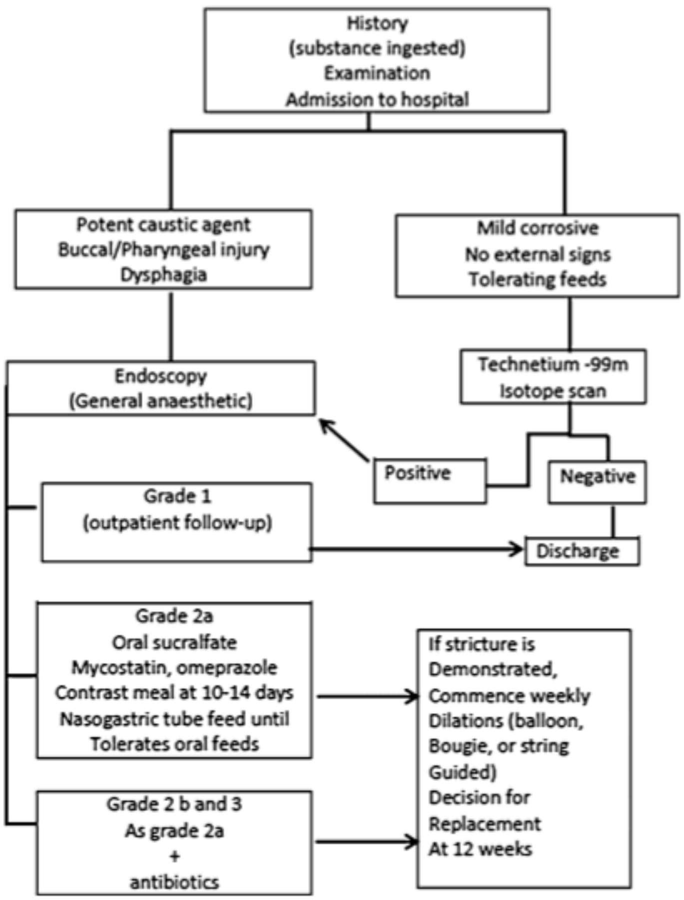

Fig. 1 Management protocol for caustic injuries of the oesophagus [11]

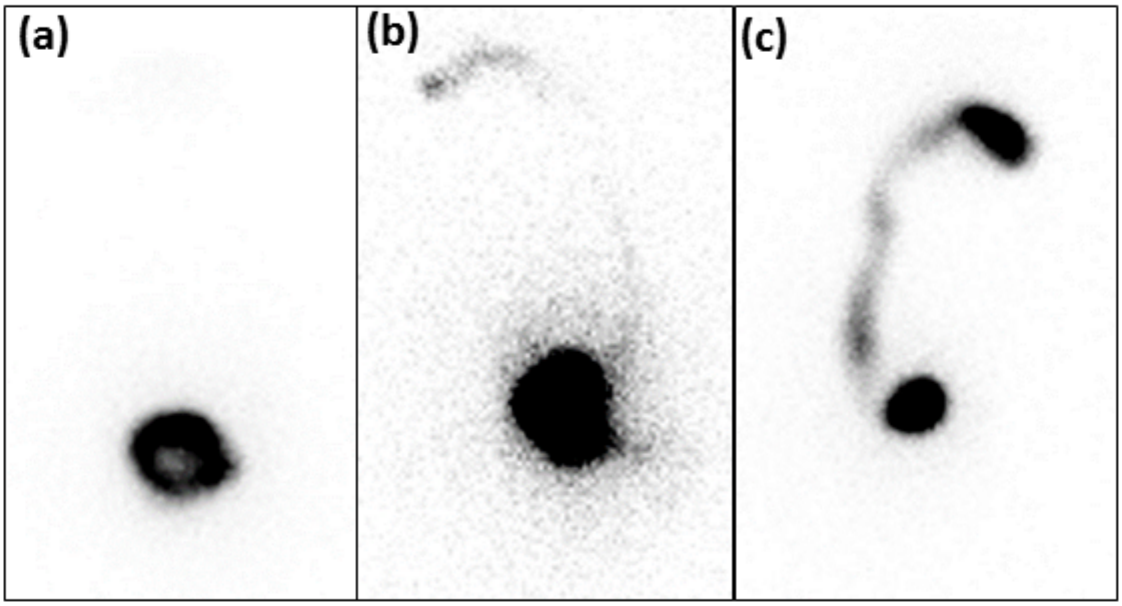

Fig. 2 99mTc Sucralfate scan showing, a) normal oesophagus with no sucralfate adhesion; b) low grade (faint) adhesion on the distal ½ of the oesophagus, and c) high grade adhesion of sucralfate on the oesophagus

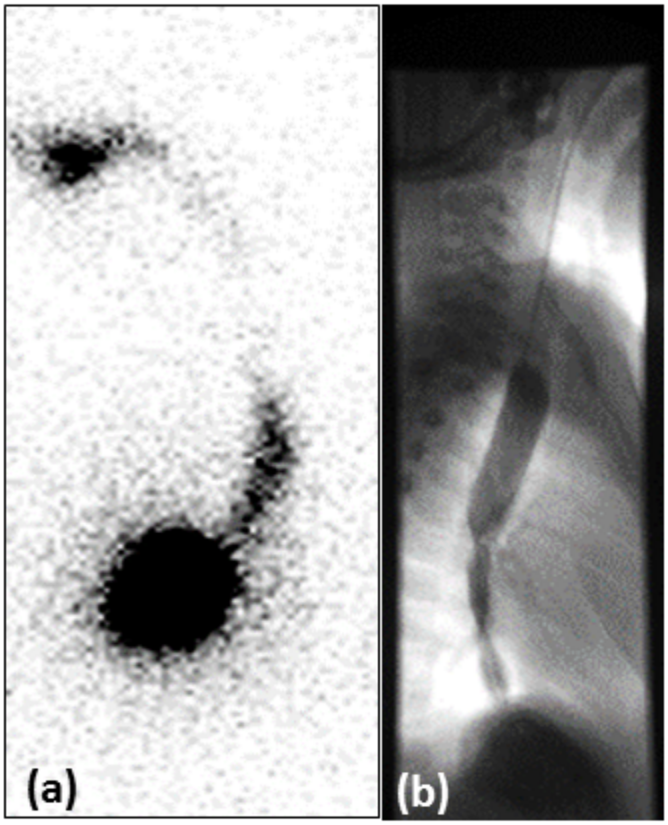

Fig. 3 Case 1. a) 99mTc Sucralfate scan showing high grade Sucralfate adhesion on the distal 1/3 of the oesophagus. Contrast swallow demonstrates b) mid–lower oesophageal stricture 3weeks post CSI

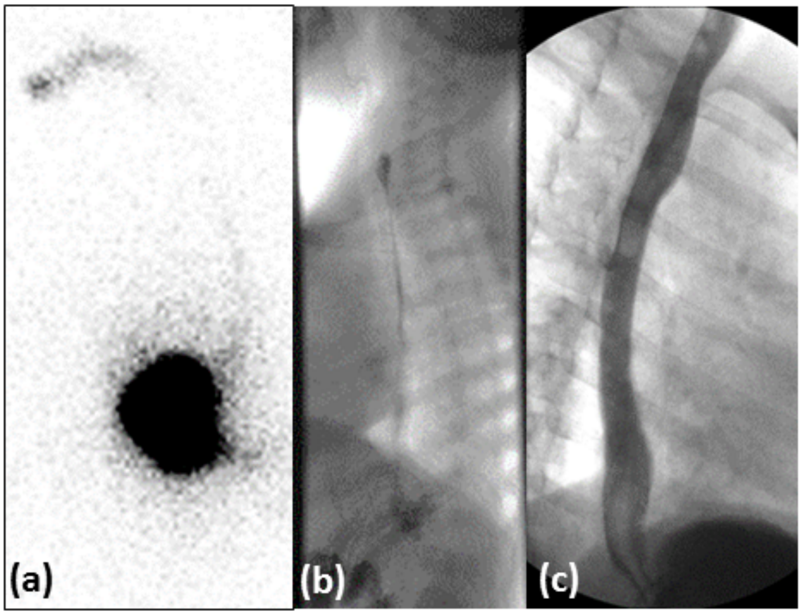

Fig. 4 Case 2. 99mTc Sucralfate scan shows high grade adhesion of Sucralfate to the entire oesophagus. Contrast swallow demonstrates a) long caustic oesophageal stricture with prestenotic dilatation, and b) normal oesophageal caliber post oesophageal dilatation program

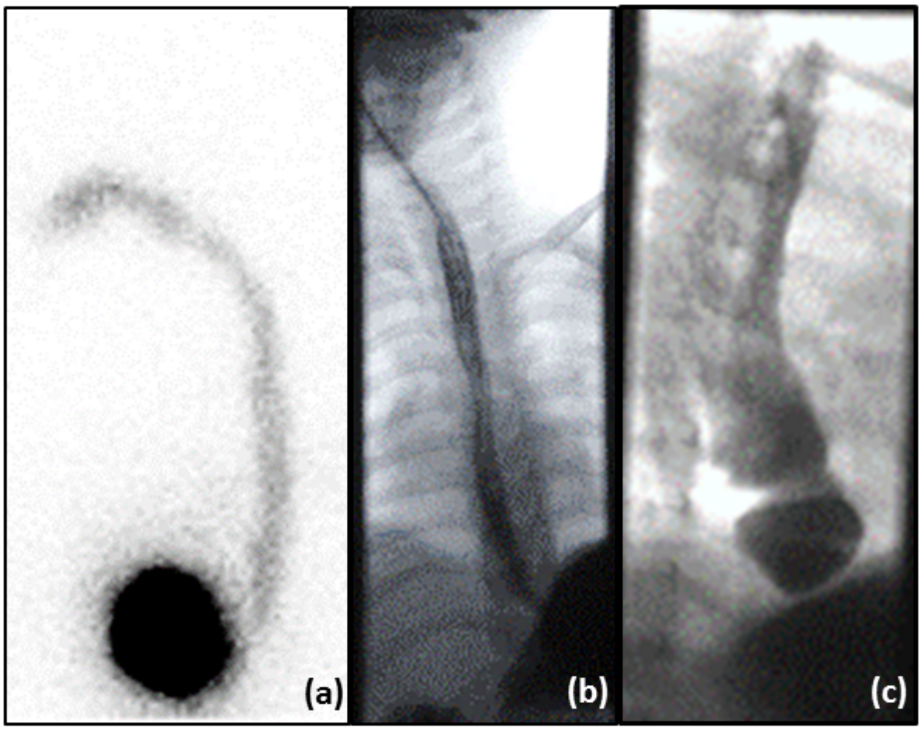

Fig. 5 Case 3: Sucralfate scan and contrast swallows: a) 99mTc Sucralfate scan showing high grade Sucralfate adhesion on the entire oesophagus; b) Contrast swallow demonstrates subtle mid oesophageal narrowing with mild mucosal irregularity extending from T4-T8, and c) colonic oesophageal replacement

CHAPTER 3

Appendix 1 - Data collection form

Weight (kg)	Symptoms	Caustic substance	Caustic substance pH (value)	99mTc labelled Sucralfate scan findings	Endoscopy findings	Time lapsed from injury to endoscopy (h)	Intervention	Further interventions e.g dilatations, replacement
10kg	Refusal to feed	floor cleaner	strong alkali (11-13)	high grade	Grade 2b *	28h	contrast swallow (07/06/2013) showed no oesophageal stricture	
8.5kg	Vomiting	bleach	oxidising reagent (12.6)	Low grade	Grade 0	6h		
11kg	Nil	cleaning solution	oxidising reagent (11-13)	Low grade	Grade 0	32h		
38.1kg	Vomiting	oven cleaner	strong alkali (13)	Low grade	Grade 1	22h		
15kg	Vomiting	bleach	oxidising reagent (12.6)	Low grade	Grade 0	28h		
28kg	Vomiting	pool acid cleaner	strong acid (3)	Low grade	Grade 1	18h		
13kg	Buccal mucosa oedema	caustic soda	strong alkali (13)	high grade	Grade 0	6h		
11.1kg	Buccal mucosa ulceration	caustic soda powder	strong alkali (13)	Low grade	Grade 2a	22h	contrast swallow (14/12/2014) showed no oesophageal stricture	
10kg	Buccal mucosa oedema + ulceration	caustic soda crystals	strong alkali (13)	Low grade	Grade 0	≤ 24h		
17.8kg	Vomiting	bleach	oxidising reagent (12.6)	Low grade	Grade 2a			
12kg	Drooling	potassium permanganate	Strong oxidising reagent	high grade	Grade 2a	25h		
	Drooling	cleaning solution	oxidising reagent (11-13)	high grade	Grade 3a *	≤ 24h		string dilatations to prograde Rusch dilatation x 23, last dilated to Rusch 32 on 05/09/2013
11kg	Drooling + Buccal mucosa oedema	hair relaxer	strong alkali (9-14)	Low grade	Grade 0	24h		
21.3kg	Drooling	jelly like toilet cleaner	oxidising reagent (1-3)	Low grade	Grade 1	29h		

9.9kg	Vomiting	bleach	oxidising reagent (11-13)	Low grade	Grade 0	21h		
13kg	Vomiting	potassium permanganate	Strong oxidising reagent	Low grade	Grade 0	30h		
15kg	Vomiting	kitchen cleaner	oxidising reagent (11-13)	high grade	Grade 2a	20h		
13kg	Buccal mucosa oedema	handy-andy (ammonia house hold cleaner)	oxidising reagent (11-12)	Low grade	Grade 1	46h		
15kg	Vomiting	toilet cleaner	oxidising reagent (1-3)	high grade	Grade 1	≤ 24h		
19.2kg	Buccal mucosa oedema + ulceration	caustic soda- drain cleaner crystals	strong alkali	Low grade	Grade 1	20h		
14kg	Drooling	peroxide	oxidising reagent (4.5-6.2)	high grade	Grade 2a	≤ 24h	Chemical pneumonitis Rx	
12kg	Vomiting and Drooling	caustic soda powder	strong alkali (13)	high grade	Grade 2b *	31h		
10kg	Vomiting	oven cleaner	strong alkali (13)	high grade	Grade 2b *	≤ 24h	contrast swallow at 3weeks: mid lower oesophagus stricture with pre-stenotic dilatation	Oesophageal dilatations from the 03/10/2013 resulted in perforation- contained leak treated non-operatively. Gastrostomy and string dilatation from 17/10/2013 x 18 dilatations + Mitomycin C application. coin lodged in mid oesophagus on 12/05/2014- removed and dilated
10.2kg	Vomiting	Oven cleaner	strong alkali (13)	Low grade	Grade 0	≤ 24h		
10.8kg	Drooling + Buccal mucosa oedema	drain cleaner	strong alkali (14)	Low grade	Grade 1	22h		
15kg	Vomiting	bleach	oxidising reagent (12.6)	Low grade	Grade 1	27h		
12kg	Vomiting	bleach	oxidising reagent (12.6)	Low grade	Grade 0	≤ 24h		
	Vomiting	bleach	oxidising reagent (12.6)	Low grade	Grade 0	≤ 24h		
11.6kg	Vomiting and Drooling	potassium permanganate	Strong oxidising reagent	high grade	Grade 0	≤ 24h		
10kg	Vomiting + Buccal mucosa oedema	hair relaxer	strong alkali (9-14) Lye + (12-14) Lye – (9-11)	Low grade	Grade 0	18h		
8.8kg	Vomiting	bleach	oxidising reagent (12.6)	Low grade	Grade 2a			
15kg	Drooling + Buccal	caustic soda granules	strong alkali (13)	low grade	Grade 0	55h		

	mucosa oedema							
13kg	Other	bleach	oxidising reagent (12.6)	Low grade	Grade 1	54h		
10kg	Vomiting	oven cleaner	strong alkali (13)	Low grade	Grade 0	≤ 24h		
9kg	Buccal mucosa oedema	handy-andy (ammonia house hold cleaner)	oxidising reagent (11-12)	Low grade	Grade 0	1h		
9.8kg	Vomiting	potassium permanganate	Strong oxidising reagent	high grade	Grade 2a	27h		
15.9kg	Vomiting	bleach	oxidising reagent (12.6)	Low grade	Grade 0	27h		
9kg	Vomiting	bleach	oxidising reagent (12.6)	high grade	Grade 0	35h		
10kg	Buccal mucosa oedema	turpentine	oxidising reagent (5.5-7.5)	Low grade	Grade 0	≤ 24h		
15.6	Drooling + Buccal mucosa oedema	stain removal product	oxidising reagent (9-10)	high grade	Grade 3a *		Gastrostomy and string placement	prograde string-Rusch dilatations x 14 colonic interposition 18/02/2015
ADDITIONAL DATA EXCLUDED FROM THE ANALYSIS								
	Drooling + Buccal mucosa oedema + ulceration	caustic soda powder	strong alkali (13)	cancelled due to URTI/LRTI and gastro-enteritis				Gastrostomy and Dilatations x 38 (between 19/04/2012 and 30/05/2013) Transmediasternal oesophago-Colonic interposition-03/07/2013 contrast swallow on D7- no leak, delayed neo-oesophagus emptying d/c on D13
13.8kg	Refusal to feed	sta-soft (Triethanolamite dieter, aminotrimethylene phosphoric acid/ dihydroxyethylm methyl ammonia sulphate)	oxidising reagent (6.5-8.5)	Not done Well on D/c				
11.2kg	Buccal mucosa oedema	hair relaxer	strong alkali (9-14) Lye + (12-14) Lye – (9-11)	Not done- 72h delay in presentation and asymptomatic. Well on D/c				
11kg	Drooling + Buccal mucosa oedema	hair relaxer	strong alkali (9-14) Lye + (12-14) Lye – (9-11)	Initial scope deferred- >72 h delay. Scoped at 4 weeks- scarrying of dist 1/3 oesophagus			at 6weeks- oral candidiasis- given nystatin. No stricture on Oesophagoscopy	

Appendix 2 - Faculty of Health Sciences Human Reseach Ethics Committee approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 January 2017

HREC REF: 049/2017

Prof A Numanoglu
Division of Paediatric Surgery
Red Cross Children's Hospital
Rondebosch

Dear Prof Numanoglu

PROJECT TITLE: CORRELATION OF SUCRALFATE SCAN AND ENDOSCOPIC GRADING IN CAUSTIC OESOPHAGEAL INJURY (MMeD-candidate- Dr B Nondela)

Thank you submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 January 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, Dr B Nondela will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC:049/2017

Appendix 3 – Information for authors

Pediatric Surgery International

Online submission and review system

Aims and Scope

Pediatric Surgery International is a journal devoted to the publication of new and important information from the entire spectrum of pediatric surgery. The major purpose of the journal is to promote postgraduate training and further education in the surgery of infants and children.

The contents will include articles in clinical and experimental surgery, as well as related fields. One section of each issue is devoted to a special topic, with invited contributions from recognized authorities. Other sections will include

Review articles
Original articles
Case reports
Technical innovations
Letters to the editor

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

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Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

Online Submission

Please follow the hyperlink "Submit online" on the right and upload all of your manuscript files following the instructions given on the screen.

Title page

Title Page

The title page should include:

- The name(s) of the author(s)
- A concise and informative title
- The affiliation(s) and address(es) of the author(s)
- The e-mail address, telephone and fax numbers of the corresponding author

Abstract

An abstract should precede the main text of each Review Article, Original Article, Technical Innovation, and Case Report. For an Original Article (max. 200 words) the abstract should be structured, i.e. divided into four paragraphs headed Purpose, Methods, Results, and Conclusion. For a Review Article (max. 200 words), Technical Innovation (max. 50 words), or Case Report (approx. 50 words), the abstract should be unstructured, i.e. in one paragraph without subheadings.

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Text

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX.

- LaTeX macro package (zip, 182 kB)

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.
Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data).
Footnotes to the title or the authors of the article are not given reference symbols.
Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Scientific style

- Please always use internationally accepted signs and symbols for units (SI units).
- Nomenclature: Insofar as possible, authors should use systematic names similar to those used by Chemical Abstract Service or IUPAC.
- Genus and species names should be in italics.
- Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention.
- Please use the standard mathematical notation for formulae, symbols, etc.:

  Italic for single letters that denote mathematical constants, variables, and unknown quantities

  Roman/upright for numerals, operators, and punctuation, and commonly defined functions or abbreviations, e.g., cos, det, e or exp, lim, log, max, min, sin, tan, d (for derivative)

  Bold for vectors, tensors, and matrices.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:
1. Negotiation research spans many disciplines [3].
2. This result was later contradicted by Becker and Seligman [5].
3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.
The entries in the list should be numbered consecutively.

- Journal article

  Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. doi: 10.1007/s00421-008-0955-8

  Ideally, the names of all authors should be provided, but the usage of “et al” in long author lists will also be accepted:

  Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. N Engl J Med 965:325–329

- Article by DOI

  Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. doi:10.1007/s001090000086

- Book

  South J, Blass B (2001) The future of modern genomics. Blackwell, London

- Book chapter

  Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

  Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

- Dissertation

Trent JW (1975) Experimental acute renal failure. Dissertation, University of California

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see

- ISSN.org LTWA

If you are unsure, please use the full journal title.
For authors using EndNote, Springer provides an output style that supports the formatting of in-text citations and reference list.

- EndNote style (zip, 2 kB)

Authors preparing their manuscript in LaTeX can use the bibtex file spbasic.bst which is included in Springer's LaTeX macro package.

Tables

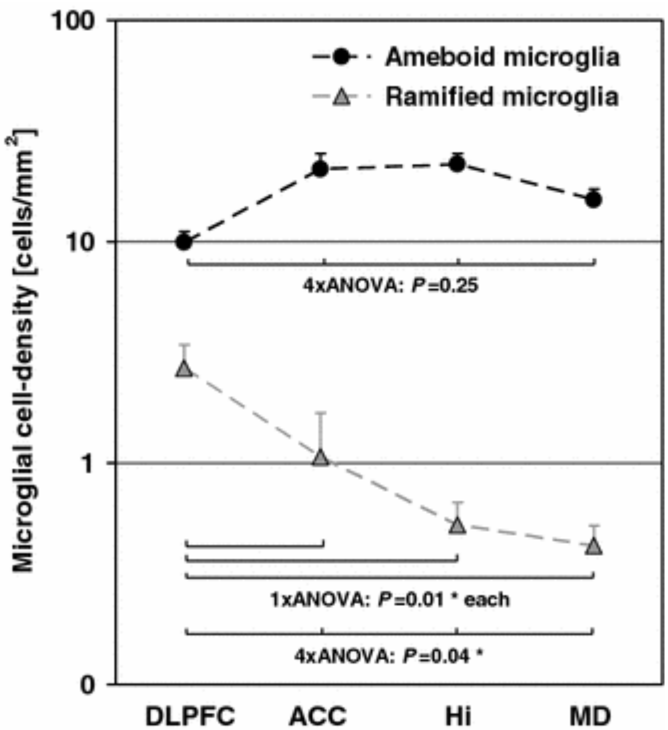
- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork and Illustrations Guidelines

Electronic Figure Submission

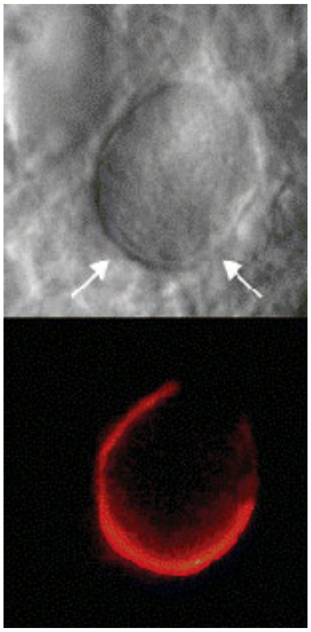
- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art



- Definition: Black and white graphic with no shading.
- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- All lines should be at least 0.1 mm (0.3 pt) wide.
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- Vector graphics containing fonts must have the fonts embedded in the files.

Halftone Art



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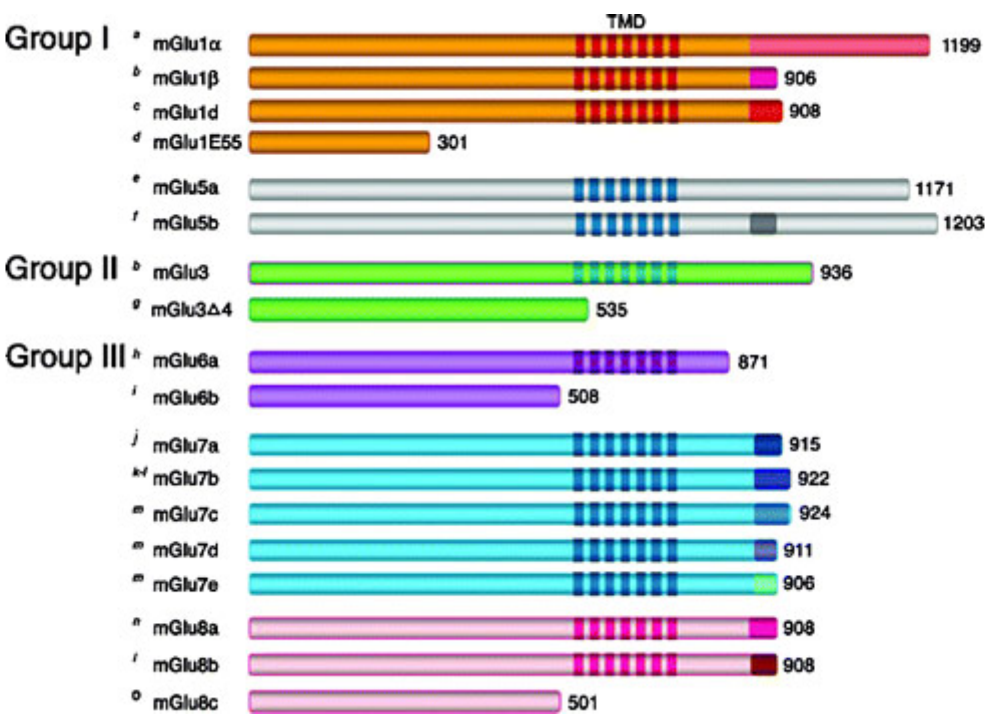
- If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.
- Halftones should have a minimum resolution of 300 dpi.

Combination Art



- Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.
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- Color art is free of charge for online publication.
- If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.
- If the figures will be printed in black and white, do not refer to color in the captions.
- Color illustrations should be submitted as RGB (8 bits per channel).

Figure Lettering

- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

Figure Numbering

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).
- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,

  "A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

Figure Captions

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.

- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

- Figures should be submitted separately from the text, if possible.
- When preparing your figures, size figures to fit in the column width.
- For most journals the figures should be 39 mm, 84 mm, 129 mm, or 174 mm wide and not higher than 234 mm.
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Submission

- Supply all supplementary material in standard file formats.
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- To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

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Text and Presentations

- Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability.
- A collection of figures may also be combined in a PDF file.

Spreadsheets

- Spreadsheets should be submitted as .csv or .xlsx files (MS Excel).

Specialized Formats

- Specialized format such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

Collecting Multiple Files

- It is possible to collect multiple files in a .zip or .gz file.

Numbering

- If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.
- Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.
- Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

Captions

- For each supplementary material, please supply a concise caption describing the content of the file.

Processing of supplementary files

- Electronic supplementary material will be published as received from the author without any conversion, editing, or reformatting.

Accessibility

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that

- The manuscript contains a descriptive caption for each supplementary material
- Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk)

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- The manuscript has not been published previously (partly or in full), unless the new work concerns an expansion of previous work (please provide transparency on the re-use of material to avoid the hint of text-recycling ("self-plagiarism")).
- A single study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g. "salami-publishing").
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- The author's institution may be informed.

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To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.
Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.
The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Disclosure of potential conflicts of interest

Authors must disclose all relationships or interests that could have direct or potential influence or impart bias on the work. Although an author may not feel there is any conflict, disclosure of relationships and interests provides a more complete and transparent process, leading to an accurate and objective assessment of the work. Awareness of a real or perceived conflicts of interest is a perspective to which the readers are entitled. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate. Examples of potential conflicts of interests **that are directly or indirectly related to the research** may include but are not limited to the following:

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- Financial support for attending symposia
- Financial support for educational programs
- Employment or consultation
- Support from a project sponsor
- Position on advisory board or board of directors or other type of management relationships
- Multiple affiliations
- Financial relationships, for example equity ownership or investment interest
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- here:

The corresponding author will include a summary statement in the text of the manuscript in a separate section before the reference list, that reflects what is recorded in the potential conflict of interest disclosure form(s).
See below examples of disclosures:

Funding: This study was funded by X (grant number X).
Conflict of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z.
If no conflict exists, the authors should state:
Conflict of Interest: The authors declare that they have no conflict of interest.

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When reporting studies that involve human participants, authors should include a statement that the studies have been approved by the appropriate institutional and/or national research ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.
If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that the independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study.
The following statements should be included in the text before the References section:
Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."
For retrospective studies, please add the following sentence:
"For this type of study formal consent is not required."

2) Statement on the welfare of animals

The welfare of animals used for research must be respected. When reporting experiments on animals, authors should indicate whether the international, national, and/or institutional guidelines for the care and use of animals have been followed, and that the studies have been approved by a research ethics committee at the institution or practice at which the studies were conducted (where such a committee exists).
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