

Clinical Practice Guidelines for Prevention, Diagnosis and Management of Early and Delayed-onset Ocular Injuries Due to Mustard Gas Exposure

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Abstract

Purpose: To develop clinical practice guidelines (CPGs) for prevention, diagnosis, treatment and follow-up of ocular injuries caused by exposure to mustard gas.

Methods: The clinical questions were designed by the guideline team. Websites and databases including National Guidelines Clearinghouse, National Institute for Clinical Excellence, Cochrane, and PubMed were searched to find related CPGs and explore possible answers to the clinical questions. Since there were no relevant CPGs in the literature, related articles in Persian and English languages were extracted. Each article along with

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Received: 23-08-2016

Accepted: 13-11-2016

Access this article online

Quick Response Code:



Website:
www.jovr.org

DOI:
10.4103/jovr.jovr_253_16

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How to cite this article: Rajavi Z, Safi S, Javadi MA, Jafarinasab MR, Feizi S, Sedighi Moghadam M, et al. Clinical practice guidelines for prevention, diagnosis and management of early and delayed-onset ocular injuries due to mustard gas exposure. J Ophthalmic Vis Res 2017;12:65-80.

its level of evidence was summarized. Additionally, hand search was performed by looking the reference list of each article. Consequently, recommendations were developed considering the clinical benefits and side effects of each therapeutic modality. The recommendations were re-evaluated in terms of customization criteria. All recommendations along with the related evidence were scored from 1 to 9 by experts from all medical universities of Iran. The level of agreement among the experts was evaluated by analyzing the given scores.

Results: The agreement was achieved for all recommendations. The experts suggested a number of minor modifications which were applied to the recommendations. Finally, CPGs were developed with 98 recommendations under three major domains including prevention of injury, diagnosis and management of the acute and delayed-onset mustard gas ocular injuries.

Conclusion: Considering the lack of CPGs for the prevention, diagnosis, and management of mustard gas-induced keratitis, these recommendations would be useful to prevent the serious ocular complications of mustard gas and standardize eye care services to the affected individuals.

Keywords: Clinical Practice Guidelines; Eye Injury; Iran; Mustard Gas

J Ophthalmic Vis Res 2017; 12(1): 65-80

INTRODUCTION

Mustard gas (MG) is a cytotoxic chemical agent with the ability to form large blisters. It is available in sulfur mustard and nitrogen mustard forms;^[1] both of them are used as a chemotherapy agent in the treatment of some dermatological diseases.^[2] While nitrogen mustard is more toxic, sulfur mustard (SM) is more common as a chemical weapon since it can remain active for a longer period of time.^[3-7]

SM was used as a chemical weapon for the first time in 1917, on a battlefield in Ypres, Belgium, during World War I.^[8-11] The majority of MG victims were inflicted during wars. In recent years, the highest rate of MG use as a chemical warfare was in the Iraq-Iran war (1980–1988).^[12,13]

MG causes severe inflammation in several tissues such as skin, eyes and respiratory tract.^[2,14,15] Because of the wet and mucosal surface of the cornea and conjunctiva and the high volume of interactions and metabolic activities of corneal epithelial cells, eye is the most sensitive tissue to SM.^[16-19] The delayed-onset MG injuries have been reported one to forty years after the initial exposure. That is why about thirty years after the end of the Iraq-Iran war; we are still faced with the incidence of new cases of delayed-onset MG ocular lesions.^[4,20-25]

In the chronic and delayed injuries, patients usually complain of photophobia, foreign body sensation and dry eye. Ophthalmic examination shows microscopic corneal abrasion, ischemic limbal area and sometimes aberrant blood vessels in the corneal periphery (pannus).^[4,21,26-29]

Decreased corneal sensation, recurrent corneal abrasions and damage to the limbal vessels lead to irregular corneal surface combined with stromal thinning.^[21,30,31] Limbal damage leads to loss of the limbal stem cells and mucin-secreting goblet cells resulting in reduced tear secretion, which is the most common complaint of patients in the chronic and delayed-onset injuries.^[32] These complications appear in almost 0.5 percent of the affected individuals who have been severely damaged during

their first exposure and usually lead to progressive and permanent visual impairment and even blindness.^[3,22]

At this time, there is no cure for SM chronic and delayed keratitis caused by and medications are mostly used as a palliative treatment.^[33,34] On the other hand, there are still new cases of delayed-onset keratitis due to MG exposure after many years have passed since the exposure and there is a possibility of using MG weapons in the future. Therefore, the evidence-based clinical practice guidelines (CPGs) for prevention, diagnosis, treatment and follow-up of early and late eye injuries due to MG were developed by the Knowledge Management Unit (KMU) of the Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences under the supervision of the Office for Healthcare Standards, Deputy of Curative Affairs, Iran Ministry of Health and Medical Education.

METHODS

The CPGs developing team included corneal fellowships, general ophthalmologists, the Head of the Center for Injured Veterans in the Iranian Foundation of Martyrs and Veterans Affairs, a PhD by research candidate (a Master of Science degree holder in optometry), the Head of the Office for Healthcare Standards, Deputy of Curative Affairs, Iran Ministry of Health and Medical Education and a Master of Science degree holder in biostatistics.

Extracting the Current Clinical Guidelines

The Guidelines International Network (G-I-N), National Institute for Clinical Excellence (NICE), National Guidelines Clearinghouse (NGC), Scottish Intercollegiate Guidelines Network (SIGN), New Zealand Guidelines Group, National Health and Medical Research Council (NHMRC), Cochrane, Bandolier, CADTH, Trip Database, PubMed, Google Scholar, SID, Medlib and Magiran were explored to extract the relevant clinical

guidelines. There were no similar CPGs in the literature. To complete the evidence, related archived articles in the Iranian Foundation of Martyrs and Veterans Affairs were also evaluated.

Designing the Clinical Questions and Extracting the Evidences

Clinical questions in the field of ocular injuries due to MG exposure were designed and the components of each clinical question {population (patients), intervention (exposure), comparison and outcome: PICO} were entered in Table 1.

Since no related CPGs was found, the evidence in English and Persian languages were extracted from the above-mentioned databases and websites using PICO to answer the questions and develop clinical recommendations.

Analyzing the Evidences

After reviewing and apprising each of the evidences, they were summarized in Table 2. The level of evidence was determined using Table 3.

Developing the CPGs Recommendations Considering Clinical Benefits and Adaptability

The CPGs developing team composed clinical recommendations by implementing the details of Table 2 and considering the clinical advantages including benefits, side effects, effect size and costs and entered them in Table 4.

Then, the adaptability of each recommendation was evaluated in Table 5 based on three criteria: 1- applicability (access to proper equipment, skills at using them, and their affordability for patient), 2- acceptability (patient's preferences, cultural considerations and patient's acceptability of the therapeutic protocol), 3-external validity (similarity between patient's characteristics/ disease type and their interference with studied evidences).

Consensus (External Review)

The recommendations along with Tables 1, 2, 4 and 5 were sent to all faculty members who were experts in this field from Baqiyatallah University of Medical Sciences, Shahid Beheshti University of Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Mashhad University of Medical Sciences, Shahed University and Shiraz University of Medical Sciences. The faculty members were asked to score the recommendations from 1 to 9 considering the clinical advantages and the adaptability criteria. They were also asked to introduce any evidence that was not included in the tables and might alter the content of the recommendations.

Evaluation of the Level of Agreement and Formulation of Final Recommendations

The scores were analyzed by the RAM model to determine the levels of agreement on each recommendation.^[35]

The agreement was achieved for all recommendations. Some of the experts suggested a number of minor modifications. After applying the modifications, 98 final recommendations were developed in three main categories: Prevention (Code A), ocular injuries in the acute phase of MG exposure (Code B), and ocular injuries in the chronic and delayed-onset phase of MG exposure (Code C), which will be presented in results section. Evidence levels (EL) have been presented for each recommendation. Appendix shows the summary of each section recommendations.

RESULTS

Code A (Prevention)

A-1- When there is the possibility of using MG, it is recommended to prevent ocular injuries by considering the following points:

A-1-1- It is recommended that all personnel carry necessary standard protective equipment including

Table 1. Analysis of recommendations

Question	P	I(E)	C	O	Type of question	Referenced guidelines	Phrase of recommendation	Level of evidence	Inconsistency of recommendations	Technical breakthrough	New systematic review	New studies
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This is the blank table template. P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes

protective mask and google, protective clothing and some potable water.^[15,36-39]

EL: III - Consensus

A-1-2- It is necessary to teach all people who are exposed to in danger of MG exposure how to use the above-mentioned equipment and how to wash their eyes in a fast and steady manner.

EL: Consensus

A-1-3- If there is a possibility of MG exposure, it is recommended to evacuate all people who their presence is not necessary in the field.^[4]

EL: IV, Consensus

A-2- In case of contacts with MG, it is recommended that the following procedures be performed immediately to reduce the eye injuries:

A- 2-1- All patients with symptoms of MG injury should immediately rinse their eyes with bathing water or normal saline for 10 to 15 minutes even if no ocular symptoms are present.^[40]

EL: IV, Consensus

A-2-2- If the clean water is not accessible, it is recommended to put a wet towel over the eyes, mouth and nose.

EL: Consensus

A-2-3-All people with any sign of toxicity should be evacuated from the field and all their clothing and equipment be removed. Then, their whole body should be washed for 10 to 15 minutes with plenty of water while their eyes are closed.

EL: Consensus

A-2-4- After washing the whole body, it is recommended to bathe the eyes again with bathing water or normal saline for 5 minutes.

EL: Consensus

A-2-5- It is recommended that all people who have been present in the field but have no signs of toxicity should remove all their clothing and equipment and wash their whole body for 10 to 15 minutes with plenty of bathing water while their eyes are closed immediately after leaving the contaminated place.^[3,41]

EL: IV

A-2-6- For those people in civilian areas (residential, factories, agricultural lands, etc.), who are asymptomatic and have been exposed to MG without using protective equipment, it is recommended to wash their eyes for 10 to 15 minutes using a normal saline solution, sodium bicarbonate solution 1.5%, Dichloramine-T 0.5%, sodium/magnesium sulfate, acide/zinc borique or with copious amounts of potable water.^[41-43]

EL: IV

A-2-7- All health care personnel who have been in contact with exposed individuals should take off all their clothes as soon as possible after the end of their mission and wash their whole body especially their eyes with bathing water.

EL: Consensus

A-2-8- It is recommended to wash the eyes without using any kind of shampoo even diluted baby shampoo.

Table 2. Analysis of the evidences

Evidence code	P	I (E)	C	O	Effect size	Statistical values	Level of evidence
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This is the blank table template. P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes

Table 3. Level of evidence

Level of evidence	Type of evidence
I	Meta-analysis Systematic reviews Randomized clinical trial
II	Clinical trial Well-designed cohort Well-designed case control Cross-sectional
III	Surveys Descriptive Case series
IV	Expert opinion, consensus

Table 4. Clinical benefits of the recommendations

Question	Phrase of recommendation	Level of evidence	Costs	Clinical effectiveness of the recommendation			Clinical effectiveness score		
				Side effects	Benefits	Effect size	Low	Moderate	High

This is the blank table template. P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes; Low: Score 1-3; Moderate: Score 4-6; High: Score 7-10

Table 5. Adaptability of the recommendations (external validity)

Question	P	I	C	O	Type of the question	Phrase of recommendation	Adaptability of the recommendation			Adaptation score	Total score
							Applicability	Acceptability	Compatibility/ External validity		
										Low	Low
										Moderate	Moderate
										High	High

This is the blank table template. P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes; Low: Score 1-3; Moderate: Score 4-6; High: Score 7-10

EL: Consensus

A-2-9- It is not recommended to put any eye patch or bandage after washing the eyes.^[43-45]

EL: IV

A-2-10- It is recommended that local anesthetic eye drops (tetracaine or proparacaine eye drops) or any other topical pain medications not be used without a prescription and medical supervision.^[46]

EL: IV

A-2-11- If artificial tears are available, it is recommended that the exposed subjects use them frequently.

EL: Consensus

A-2-12- It is recommended that the health care personnel anesthetize the affected individuals' eyes with the topical eye drops, insert a eyelid speculum and wash them for 10 to 15 minutes using normal saline or potable water.

EL: Consensus

A-2-13- If ocular pain is present, systemic analgesics should be prescribed under the supervision of medical personnel.

EL: Consensus

A-2-14- For the prevention of secondary infection, antibiotic eye drops are recommended (chloramphenicol or ciprofloxacin) every 6 hours for one week under the supervision of medical staff.^[39]

EL: IV

A-2-15- It is recommended to wash all washable equipment in the health care center being involved in treating exposed subjects at the end of the day. The equipment which is not washable should be cleaned.

EL: Consensus

A-2-16- All objects in contact with MG should be placed in sturdy and durable polyethylene containers with a thickness of 6-mil and disposed of, to prevent the spread of MG contamination.^[47]

EL: Consensus

A-2-17- Stability of MG is higher in cold regions, while in hot regions its stability is reduced. But due to rapid

evaporation in hot regions, the concentration will increase. It is recommended that all people who are exposed to the MG, leave the infected areas as soon as possible.

EL: Consensus

Code B (Acute Phase of Ocular Injuries due to MG Exposure)

B-1- According to the internal consensus, the signs and symptoms of acute eye injuries were divided into three forms of mild, moderate and severe [Figure 1]

B-1-1- Patients with the following signs and symptoms of acute ocular injuries should be regarded as the mild form:^[39,40,48]

Symptoms

Foreign body sensation in eyes, tearing, photophobia, blepharospasm

Signs

Eyelids hyperemia, vascular dilation and hyperemia of the conjunctiva, lack of corneal involvement

EL: IV- Consensus

B-1-2- Patients with the following signs and symptoms of acute ocular injuries should be regarded as the moderate form:^[25,39,48]

Symptoms

Same as mild injury, plus any of the following symptoms:

Dry eye sensation, eye pain

Signs

Same as mild injury, plus any of the following signs:

Conjunctival edema, corneal epithelial edema, corneal epithelial erosion, superficial punctate keratopathy (more in the lid fissure area)

EL: IV- Consensus

B-1-3- Patients with the following signs and symptoms of acute ocular injuries should be regarded as the severe form:^[25,39,40,48,49]

Symptoms

Same as mild and moderate injuries, plus any of the following symptoms:

Severe ocular pain, swelling, redness, sores and spasms of the eyelids, reduced vision

Signs

Same as mild and moderate injuries, plus any of the following signs:

Inflammation, edema and in some cases, secondary infection of the conjunctiva, ischemia and necrosis of the conjunctiva, limbal ischemia and necrosis, corneal epithelial irregularity and defect, corneal stromal edema, possible corneal infection, inflammation of the anterior chamber (uveitis), perforation of the cornea

EL: IV- Consensus

Important Recommendations

It should be noted that the symptoms of acute ocular injuries may range from the least to the most severe forms:

Eyelids: From swelling and redness to blepharospasm
 Conjunctiva: From redness and foreign body sensation to severe chemosis
 Cornea: From foreign body sensation to severe visual reduction and pain

It should also be noted that the signs of acute ocular injuries may be seen from the least to the most severe forms:

Eyelids: From hyperemia to ulcer and necrosis
 Conjunctiva: From hyperemia to necrosis
 Limbus: From hyperemia to necrosis
 Cornea: From normal to corneal perforation

B-2- Diagnostic recommendations for the acute ocular injuries (mild, moderate and severe forms)

B-2-1- It is recommended that all personnel use MG detectors as soon as the use of chemical weapons is speculated to make a definitive diagnosis and rule out possible differential diagnoses.^[49-52]

EL: IV- Consensus

B-2-2- Since there is no laboratory test to definitively diagnose the acute phase, it is recommended that the diagnosis of this phase be determined by precise evaluation of the clinical signs and symptoms.^[49-52]

EL: IV- Consensus

B-3- Treatment recommendations for the acute phase ocular injuries (mild, moderate and severe forms)

B-3-1- Mild form:

B-3-1-1- The eyes should be washed with abundant potable water immediately after MG exposure. In case of no access to potable water, any type of water (such as ponds, streams) can be used.

EL: Consensus

B-3-1-2- Topical antibiotics eye drops should be prescribed (e.g., chloramphenicol or ciprofloxacin eye drops every 6 hours to prevent bacterial infection).^[7,38,52-54]

EL: IV- Consensus

B-3-1-3- Corticosteroids eye drops should be administered every 8 to 12 hours for a week.^[38,52]

EL: IV- Consensus

B-3-1- 4- Artificial tears and lubricants should be administered every 6 hours.^[7,38,52-54]

EL: IV- Consensus

B-3-1- 5- Wearing sunglasses

B-3-2- Moderate form (starred ones are similar to the mild form):

B-3-2-1- Washing eyes with abundant potable water immediately after gas exposure and in case of no access to potable water, any bathing water (such as ponds, streams) should be used.*

EL: IV- Consensus

B-3-2-2- Topical antibiotics eye drops should be prescribed (e.g., ophthalmic chloramphenicol or ciprofloxacin* every 6 hours to prevent bacterial infection).^[7,38,52-54]

EL: IV- Consensus

B-3-2-3- Corticosteroids eye drops* should be administered every 6 to 8 hours for a week.^[38,52]

EL: IV- Consensus



Figure 1. Ocular injuries due to mustard gas exposure in acute phase. Reproduced from “Javadi MA, Feizi S. Mustard gas ocular injuries in chemical warfare victims. 1st ed. Tehran: FARHANG FARDA; 2014”.

B-3-2-4- Artificial tears with no preservatives (ocular lubricants)* should be administered every 4 to 6 hours.^[7,38,52-54]

EL: IV- Consensus

B-3-2-5- Oral analgesics should be used under medical supervision if pain is present.

EL: Consensus

B-3-2-6- Wearing sunglasses*

B-3-3- Severe form (starred ones are similar to the mild and moderate forms):

B-3-3-1- Eyes should be washed with abundant potable water immediately after gas exposure and in case of lack of access to potable water, any bathing water (such as ponds, streams) should be performed.*

EL: IV- Consensus

B-3-3-2- Topical antibiotics eye drops should be prescribed every 6 hours for a week to prevent bacterial infection.*

EL: Consensus

B-3-3-3- In the absence of conjunctival and corneal infections, corticosteroids eye drops* should be administered (one drop every 4 to 6 hours for a week and then reduce the dose as needed).^[38]

EL: IV- consensus

B-3-3-4- Artificial tears with no preservatives (ocular lubricant)* should be administered every 2 to 4 hours.^[7,38,52-54]

EL: IV- consensus

B-3-3-5- Bandage contact lens (in the presence of a large defect in the corneal epithelium and absence of dry eye and severe ischemia and corneal or conjunctival infection).^[38]

EL: IV

B-3-3-6- Oral Doxycycline capsule (100 mg every 12 hours for 2 weeks and then as required).^[52]

EL: IV

B-3-3-7- Oral analgesics should be used under medical supervision if pain is present*

EL: Consensus

B-3-3-8- Wearing sunglasses*

B-3-3-9- If there is any suspicion of secondary bacterial or fungal conjunctivitis, conjunctival specimen should be evaluated and then broad-spectrum antibiotics (e.g., ciprofloxacin eye drop) should be prescribed every one hour. Thereafter, the type and dosage of antibiotics should be adjusted based on the patient's response and the antibiogram results.

EL: Consensus

B-3-3-10- If any signs and symptoms of corneal infection are present, evaluating an immediate corneal specimen is recommended and depending on the severity of keratitis, fortified broad-spectrum antibiotics like gentamicin (14 mg per mL) eye drop, cefazolin (50 mg per ml) or vancomycin eye drop and ceftazidime eye drop every 5 to 15 minutes for an hour and then every half an hour for 24 hours should be started. Best antibiotic medication and its dosage should be adjusted depending on the patient's response and the antibiogram results.

EL: Consensus

B-3-3-11- If there is no response to treatment and perforation of the cornea happens, the following actions should be considered:

B-3-3-11-1- If the perforation diameter is equal to or less than 2 mm, in the absence of corneal infection and iris prolapse, applying cyanoacrylate glue and a bandage contact lens along with antibiotic eye drops and intravenous antibiotics are recommended.

EL: Consensus

B-3-3-11-2- If the perforation diameter is more than 2 mm or in the presence of iris prolapse, penetrating keratoplasty (PK) is recommended to protect the eye.

EL: Consensus

B-4- Follow-up recommendations for the acute ocular injuries (mild, moderate and severe forms)

B-4-1- Mild form: It is recommended that the next visit be performed one week after the diagnosis unless symptoms are intensified.

EL: Consensus

B-4-2- Moderate form: Daily visit is recommended until corneal symptoms are subsided and then weekly visit up to improvement of the conjunctiva and the eyelids.^[38]

EL: IV -Consensus

B- 4-3- Severe form: It is recommended that the patients be hospitalized. Otherwise daily visit should be scheduled until complete healing of the corneal lesions are observed.^[38]

EL: IV - Consensus

B-4-3-1- In case of infection or perforation of the cornea, the patient must be admitted to a hospital for treatment.

EL: Consensus

Code C (Chronic and Delayed-onset Ocular Injuries due to MG Exposure)

C-1- According to the internal consensus, the signs and symptoms of chronic and delayed-onset ocular injuries were divided into three forms; mild, moderate and severe [Figure 2]

C-1-1- Patients with the following signs and symptoms of the chronic and delayed ocular injuries should be regarded as the mild form:^[18,22,27,37,39,40,48,55-60]

Symptoms

Photophobia, burning, foreign body sensation in eyes, dry eye, tearing, and slight redness of the eye

EL: II- Consensus

Signs

Meibomian gland dysfunction, chronic blepharitis, reduced thickness of the tear meniscus layer, telangiectasia of the conjunctival blood vessels, comma shape vascular

tortuosity in the palpebral fissure area (nasal and temporal), subconjunctival fibrosis, subconjunctival hemorrhage, scarring of the conjunctiva, punctate epithelial erosions

EL: II – Consensus

C-1-2- Patients with the following signs and symptoms of the chronic and delayed ocular injuries should be regarded as the moderate form:^[22,27,37,39,40,44,48,55-60]

Symptoms

Same as mild injury, together with any of the following symptoms:

Reduced vision, marked red eye, itchy eyes, ocular pain

EL: II - Consensus

Signs

Same as mild injury, together with any of the following signs:

Corneal irregular astigmatism, periods of relapse and remission, mild to moderate limbal ischemia, irregular cornea, thinning of the corneal periphery, corneal opacity as well as lipid and amyloid material and deposition in the corneal periphery, peripheral corneal vascularization, peripheral stromal scars of the cornea, peripheral intra-corneal hemorrhage, transparency of the corneal center, decreased corneal sensation

EL: II - Consensus

C-1-3- Patients with the following signs and symptoms of the chronic and delayed ocular injuries should be regarded as the severe form:^[18,22,37,39,40,48,55,60-62]

Symptom

Same as mild and moderate injuries, in addition to any of the following symptom:

Severe photophobia, severe vision loss, severe pain

EL: II- Consensus

Signs

Same as mild and moderate injuries, in addition to any of the following signs:

Severe limbal ischemia, limbal cell deficiency, thinning and opacity of the central and peripheral parts of the cornea, corneal opacity as well as lipid and amyloid deposition in the cornea, central and peripheral corneal vascularization, band keratopathy and scars in the central and peripheral corneal stroma, central and peripheral intra-corneal hemorrhage, corneal conjunctivalization, corneal descemetocele, corneal ulcer, corneal melting and perforation, history of limbal and corneal surgeries

EL: II – Consensus

Further Recommendations

Although our experience over the past 30 years suggests no direct relationship between mustard gas exposure

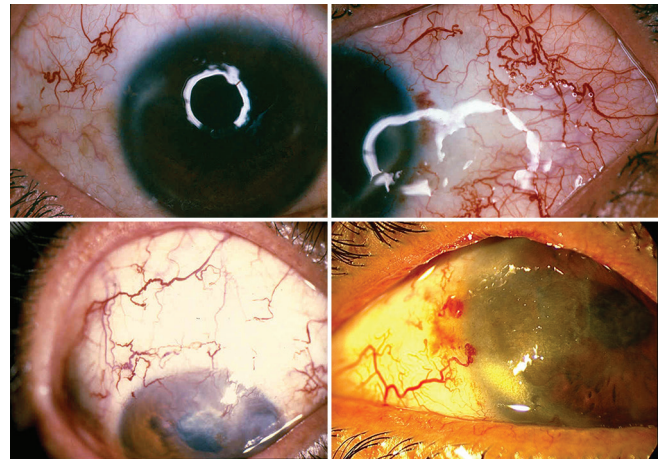


Figure 2. Chronic and delayed-onset ocular injuries due to mustard gas exposure. Reproduced from “Javadi MA, Feizi S. Mustard gas ocular injuries in chemical warfare victims. 1st ed. Tehran: FARHANG FARDA; 2014”.

and development of glaucoma, cataract, vitreoretinal and optic nerve disorders in the chronic phase, it is recommended that all patients with a history of intraocular surgery or those who are receiving long-term steroid therapy, be evaluated for these ocular diseases.

EL: Consensus

C-2- Diagnostic recommendations for the chronic and delayed-onset ocular injuries (mild, moderate and severe forms)

C-2-1- Chronic inflammation, overriding of the conjunctival epithelium to the cornea, decreased conjunctival goblet cells and epithelial thinning can be observed using an optical microscope. Electron microscopy shows destruction of the corneal basement membrane and cytoplasmic vacuolization but fluorescence microscopy findings are nonspecific. Routine biopsy is not recommended for detection of MG keratopathy unless during the surgical treatment.^[38,63]

EL: III- Consensus

C-2- 2- Confocal microscopy findings include decreased thickness of the cornea, thinning and irregularity of the epithelium and basal layer as well as reduced number of stromal keratocytes, presence of spindle shape keratocytes, hyper-reflective deposits in the stroma and reduced endothelial cells. Endothelial changes are not significant.^[38,64-65]

EL: II

C-2-3- In all patients with MG keratopathy with clinical signs, limbal cell defects can be detected by impression cytology during the chronic phase. Sometimes, these findings do not match with the clinical symptoms. Therefore, impression cytology is not usually recommended unless the clinical diagnosis is not sufficient.^[50,66]

EL: III- Consensus

C-2-4- Laboratory methods for measuring white blood

cells, polymorphonuclear leukocytes, the level of hydrogen peroxide, inflammatory cytokines (interleukin -1Ra, interleukin1beta, interleukin 1 alpha, tumor necrosis factor), serum levels of syllable period-selective, red blood cells, platelets, C-reactive protein, Rheumatoid factor, matrix metalloproteinase 9, serum C3, C4, natural killer cells, Immunoglobulin M, Immunoglobulin F and Immunoglobulin E have been evaluated in several studies for diagnosis of ocular disorders in chronic phase, but none are specific for MG exposure and are not usually recommended.^[40,67-73]

EL: II- Consensus

Serum levels of cytokines in people who have been exposed to MG is less than the control group even 20 years after exposure. But since this is a common finding in many chronic diseases, this test is not usually recommended.^[68]

EL: II- Consensus

Generally, these tests are not recommended in cases where the clinical diagnosis of MG exposure is certain. But they can be useful in cases where the clinical signs are not sufficient for diagnosis.

C-3- Treatment recommendations for the chronic and delayed-onset ocular injuries (mild, moderate and severe forms)

C-3-1- Mild form:

C-3-1-1- Wearing appropriate sunglasses especially for people who live in dry and sunny environments.

EL: Consensus

C-3-1-2- Supplying more moisture in the living environment or to live in the humid areas.

EL: Consensus

C-3-1-3- Artificial tears and ocular lubricants with or without preservatives (1 to 4 times a day).^[22,27,38]

EL: II - Consensus

C-3-1-4- Topical treatment for blepharitis (warm compresses, shampoo scrubs, topical antibiotics). In cases resistant to topical therapy, systemic antibiotics (tetracycline, azithromycin, and doxycycline) are recommended.^[74]

EL: II- Consensus

C-3-1-5- Temporary punctual occlusion^[22,27,29-31]

EL: II- Consensus

C-3-2- Moderate form (starred items are similar to the mild form):

C-3-2-1- Appropriate sunglasses should be worn especially for people who live in dry and sunny environments.*

EL: Consensus

C-3-2-2- Supplying more moisture in the living environment or to live in the humid areas.*

EL: Consensus

C-3-2-3- Prescribing artificial tears and lubricants eye drop with no preservatives (1 to 4 times a day).^{[22,27,38]*}

EL: II- Consensus

C-3-2-4- Topical treatment of blepharitis (warm compresses, shampoo scrubs, topical antibiotics). In cases resistant to topical therapy, systemic antibiotics (tetracycline, azithromycin, and doxycycline) are recommended.^{[74]*}

EL: II - Consensus

C-3-2-5- Temporary* or permanent punctual occlusion^[22,27,29-31]

EL: II - Consensus

C-3-2-6- Tarsorrhaphy in case of severe dry eye^[22,27]

EL: II

C-3-2-7- Prescribing the corticosteroids eye drops with control of possible complications or topical cyclosporine A (0.05%) (Twice a day)^[22,27,29-30,38,75]

EL: II

C-3-2-8- In cases with significant peripheral corneal thinning who present with noticeable symptoms such as redness, tearing, decreased visual acuity and risk of corneal perforation, keratolimbal allograft surgery is recommended.^[31]

EL: II

C-3-2-9- In cases where corneal pathology is present in the periphery (thinness and moderate to severe ischemia of the conjunctiva), conjunctival advancement surgery is not recommended.^[38]

EL: IV

C-3-3- Severe form (starred items are similar to the mild or moderate forms):

C-3-3- 1- medical treatments:

C-3-3-1-1- Wearing sunglasses*

EL: Consensus

C-3-3-1- 2- Supplying more moisture in the living environment or living in the humid areas*

EL: Consensus

C-3-3-1-3- Prescribing artificial tears and lubricant eye drops with no preservatives (1 to 4 times a day)^[22,27,38]

EL: II- Consensus

C-3-3-1- 4- Topical treatment of blepharitis (warm compresses, shampoo scrubs, topical antibiotics). In cases resistant to topical therapy, systemic antibiotics (tetracycline, azithromycin, and doxycycline) are recommended.^{[74]*}

EL: II - Consensus

C-3-3-1-5- Temporary or permanent punctual occlusion^{[22,27,29-31]*}

EL: II

C-3-3-1-6- Prescribing topical corticosteroids with control of possible complications or topical cyclosporine A (0.05%) (Twice a day).^{[22,27,29-31]*}

EL: II

C-3-3- 2- Surgical treatments:

C-3-3-2-1- Tarsorrhaphy in case of severe dry eye^{[22,27]*}

EL: II

C-3-3-2-2- If epithelial defect is resistant to medical treatment, it is recommended to perform amniotic membrane transplantation in addition to tarsorrhaphy.^[22,31]

EL: II

C-3-3-2-3- In case of ischemia and thinning of the cornea and the sclera adjacent to it, keratolimbal allograft is recommended.^[31,74,76]

EL: II

C-3-3-2-4- If stem cell transplantation is needed, keratolimbal method is preferable to using stem cells from first-degree relatives.^[27]

EL: II

C-3-3-2-5- In case of ischemia coupled with thinning of the cornea, sclera and limbus combined with central corneal epithelial cells deficit, combined surgery of amniotic membrane transplantation and limbal stem cell transplantation is recommended.^[31]

EL: II

C-3-3-2-6- In cases of epithelial defect resistant to medical treatment it is recommended to administer bandage contact lens while doing other treatments.

EL: Consensus

C-3-3-2-7- If the opacity has affected the central cornea and normal endothelial cells are present, lamellar transplantation is preferred.^[30]

EL: II

C-3-3-2-8- Deep anterior corneal transplantation with big bubble technique is not recommended in these patients and the conventional method is preferred.^[27,31]

EL: II

C-3-3-2-9- If lamellar graft of the cornea and limbal stem cell transplantation is needed, combined surgery is preferable to the sequential surgery.^[31]

EL: II

C-3-3-2-10- In case of corneal perforation and endothelial cells damage, it is recommended to perform PK.^[30]

EL: II

C-3-3-2-11- If both PKP and stem cell transplantation are indicated, it is advisable to perform stem cell transplantation first followed by PKP after a few months (combined surgery is not recommended).^[29]

EL: III

C-4- Follow-up recommendations related in the chronic and delayed-onset ocular injuries (in mild, moderate and severe forms)

C-4-1- Mild form:

C-4-1-1- If symptoms have not changed in the course of the disease, it is recommended that patients be examined every year.

EL: Consensus

C-4-1-2- If a change in symptoms or signs is noticed by the patient or the physician, it is recommended to perform eye examinations at appropriate intervals.

EL: Consensus

C-4-2- Moderate form (starred ones are similar to the mild form):

C-4-2-1- If medical treatment is adequate for the

patient and the patient's condition is stable, it is recommended the patient be followed every 6 months.

EL: Consensus

C-4-2-2- If a change in symptoms or signs is observed by the patient or the physician, it is recommended to perform eye examinations at appropriate intervals.*

EL: Consensus

C-4-2-3- Patients who undergo keratolimbal surgery should be followed according to the known protocol for keratolimbal surgery (visit on the first and third days, first week, second week, first, second and third months and then every 3 months in the first year and then every 6 months). In case of patient's complaints or any unusual finding in ocular examination, patient should be followed at appropriate intervals.

EL: Consensus

C-4-2-4- It is recommended that medical therapy, especially systemic steroids and immunosuppressive medications be prescribed in collaboration with a nephrologist or an oncologist.

EL: Consensus

C-4-3- Severe form (starred ones are similar to the mild and moderate forms):

C-4-3-1- If the patient's condition is stable; it is recommended the patient be followed every 3 months.

EL: Consensus

C-4-3-2- If a change in symptoms or signs is observed by the patient or the physician, it is recommended to perform eye examinations at appropriate intervals.*

EL: Consensus

C-4-3-3- Patients who have a history of surgery should be followed based on the type of surgery.

EL: Consensus

DISCUSSION

Considering severe ocular injuries due to MG exposure, Iran's unique experience in this field and the lack of similar CPGs in the world, these CPGs were developed in KMU, Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences under the supervision of the Iranian Ministry of Health and Medical Education with a total of 98 recommendations.

Due to the importance of appropriate diagnosis and treatment of the affected patients and the lack of standard procedures for patient management, all experts in this field who had practically managed and followed chemically injured patients for many years were invited to participate as a member of the CPGs developing team or an external reviewer (consensus).

An agreement score was achieved for all recommendations developed by the CPGs developing team in the external review. Then, these recommendations were considered as final recommendations after minor editing suggested by the experts.

Due to critical war conditions, high level evidence such as meta-analyses, systematic reviews, and clinical trials on the management of acute MG injury is limited in the literature and most of the data is not based on strong methodology. Moreover, most of the evidence related to ocular injuries due to MG exposure in chronic and delayed onset injuries is also confined. Published review articles are not systematic reviews and are written by experts in the field as narrative reviews.

Since most evidence of ocular injuries due to MG exposure has been critically reviewed in this project, we believe it will be helpful to perform well-designed research projects in the future.

In conclusion, the CPGs for the “prevention, diagnosis, treatment and follow-up of early and late eye injuries due to mustard gas” will promote the standardization of the prevention, diagnosis, treatment and follow-up of the affected patients at national and international levels.

Acknowledgements

This research was supported by Janbazan Medical and Engineering Research Center, Tehran, Iran. We are immensely grateful to the faculty members of all universities for scoring the recommendations of this clinical practice guideline. We thank Mr. Saeed Rahmani for his valuable assistance. We also appreciate Ms. Soheila Khoshneshin’s technical assistance.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

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APPENDIX: SUMMARY OF RECOMMENDATIONS

Code A (Prevention) recommendations

Before exposure to MG	<ul style="list-style-type: none"> • Having protective equipment (standard mask, protective cloths) • Carry some potable water • Washing eyes constantly and quickly after exposure to MG • Civilian personnel should be evacuated from the area
Immediately after exposure to MG	<ul style="list-style-type: none"> • Washing eyes fast and consistently with water (potable water is preferred). Using shampoo is not recommended. • Using artificial tears and lubricant eye drops • Using antibiotic eye drops • Do not apply any eye pad • Take off all clothes • Bathing the whole body • Leaving the contaminated area quickly
MG, mustard gas	

Code B (Acute ocular injuries due to MG exposure) recommendations

Mild (Conjunctival involvement)	<p>Symptoms: Tearing, foreign body sensation, photophobia, blepharospasm</p> <p>Signs: Hyperemia of eyelids and conjunctival vasodilation and hyperemia, lack of corneal involvement</p> <p>Treatment: Washing the eyes, using antibiotic eye drops, artificial tear and lubricant eye drops, topical corticosteroids and wearing sunglasses</p> <p>Follow-up: A week after initial examination</p>
Moderate (Conjunctival and superficial corneal involvement)	<p>Symptoms: Same as mild form in addition to eye pain and dry eye sensation</p> <p>Signs: Those of mild form plus conjunctival edema, swelling of the corneal epithelium, superficial punctate keratopathy, superficial corneal aberrations</p> <p>Treatment: Same as mild form plus the use of oral analgesics</p> <p>Follow-up: Daily until corneal symptoms improve</p>
Severe (Conjunctival and deep corneal layers involvement)	<p>Symptoms: Same as mild and moderate symptoms in addition to eyelid redness, swelling, scarring and eyelids spasms, loss of vision</p> <p>Signs:</p> <p>Same as mild and moderate plus any following signs:</p> <ul style="list-style-type: none"> • Conjunctiva: secondary infection, ischemia, necrosis • Limbus: ischemia, necrosis • Cornea: stromal edema, secondary infection, perforation • Uvea: uveitis <p>Treatment: Treatment of moderate form plus:</p> <ul style="list-style-type: none"> • Bandage contact lens (BCL) in case of large corneal epithelial defects without severe dryness or conjunctival and corneal infection • Oral doxycycline <p>Conjunctivitis → culture → broad-spectrum antibiotics</p> <p>Corneal infection → culture → fortified broad-spectrum antibiotic eye drops</p> <p>Perforation of cornea less than 2 mm without iris prolapse → cyanoacrylate glue + BCL</p> <p>Perforation of cornea more than 2 mm with iris prolapse → corneal transplantation</p> <p>Follow-up:</p> <ul style="list-style-type: none"> • Active corneal lesions: <ul style="list-style-type: none"> • Hospital admission if possible • Daily visits • Corneal perforation: <ul style="list-style-type: none"> • The patient must be hospitalized • Daily visits
Diagnostic procedures for all three forms	<ul style="list-style-type: none"> • Using MG detector if the existence of other gases is suspicious • Using clinical signs and symptoms to diagnose acute phase and severity of the injury <p>Conclusion: Paraclinical and laboratory testing in the acute phase is not necessary</p>
MG, mustard gas	

Code C (Chronic and delayed-onset ocular injuries due to MG exposure) recommendations

Mild (Eyelid, conjunctival and superficial corneal involvement)	<p>Symptoms: Foreign body sensation, dry eye, tearing, mild redness, photophobia, eye irritation</p> <p>Signs:</p> <ul style="list-style-type: none"> • Eyelids: Meibomian gland dysfunction, blepharitis • Tears: Reduction of tear meniscus layer • Conjunctiva: Telangiectasia, vascular tortuosity mostly in the lid fissure, subconjunctival bleeding, fibrosis, scar • Cornea: Punctate epithelial erosions <p>Treatment:</p> <ul style="list-style-type: none"> • Using sunglasses • Living in wet climate • Artificial tear eye drops • Topical treatment of blepharitis (warm compress, scrub with shampoo, topical antibiotics). In patients who are resistant to topical antibiotics, oral antibiotics such as erythromycin or doxycycline can be prescribed. • Temporary punctal occlusion <p>Follow-up:</p> <ul style="list-style-type: none"> • Annual follow-up if symptoms are stable • In the event of any new complaint, ophthalmic examination is recommended in short intervals
Moderate (Eyelid, conjunctival limbal and peripheral corneal involvement)	<p>Symptoms: Same as mild form plus reduced vision, significant eye redness, itching and ocular pain</p> <p>Signs: Signs of mild form plus:</p> <ul style="list-style-type: none"> • Limbus: Mild to moderate ischemia, limbal stem cells deficiency • Cornea: Corneal epithelial irregularity, irregular corneal astigmatism, peripheral corneal thinning, peripheral corneal opacity, lipid and amyloid deposition, peripheral corneal neovascularization, peripheral corneal hemorrhage, decreased corneal sensation, transparency of the central cornea, periods of relapse and remission of symptoms <p>Treatment: Same as mild form in addition to:</p> <ul style="list-style-type: none"> • Temporary or permanent punctal occlusion • Tarsorrhaphy • Prescribing corticosteroid eye drop or topical cyclosporine A (0.05%) twice daily • In the event of significant peripheral corneal thinning with symptoms such as redness, tearing and risk of corneal perforation, keratolimbal allograft should be performed • Do not perform conjunctival advancement surgery in presence of any peripheral corneal pathology <p>Follow-up:</p> <ul style="list-style-type: none"> • Follow-up every six months if symptoms are stable • If keratolimbal surgery is performed, a routine follow-up is enough for this type of surgery • Prescription or discontinuation of medications should be performed by the ophthalmic surgeon associated with nephrology and/or oncology consultation • In the event of any new complaint, short interval visits are recommended
Severe (Eyelid, conjunctival, limbal and peripheral as well as central corneal involvement)	<p>Symptoms: Same as mild and moderate forms plus severe vision loss, photophobia, intense pain</p>

Contd...

Code C (Contd...)

Signs: Same as mild and moderate forms together with central corneal thinning, corneal opacity, corneal deposits, corneal neovascularization, corneal hemorrhage, band-shaped keratopathy, microbial ulcer, corneal melting, dermatocele, corneal perforation and conjunctivalization

Treatment: Same as mild and moderate forms plus:

Medical: Same as moderate form

Surgical:

- Tarsorrhaphy
- In case of persistent corneal epithelial defect: tarsorrhaphy and amniotic membrane transplantation
- In presence of corneal periphery, limbal and scleral thinning: keratolimbal allograft transplantation
- If limbal stem cell transplantation is required, keratolimbal method is preferred to using stem cells from first-degree relatives
- In case of corneal, limbal and adjacent scleral thinning and ischemia with corneal epithelial defect, combined limbal stem cells and amniotic membrane transplantation is recommended
- In case of central corneal opacity without endothelial involvement, lamellar keratoplasty is preferred to penetrating keratoplasty (PK)
- In case of central corneal opacity without endothelial involvement, standard lamellar keratoplasty is preferred to big-bubble technique
- If the limbal stem cell transplantation and lamellar keratoplasty technique are required, simultaneous surgery is preferred to sequential operation
- If PK and stem cells transplantation are needed, it is recommended to perform limbal stem cell transplantation ; PK should be performed several months later

Follow-up:

- Follow- up every 3 months in case of response to medical treatment and stabilization of symptoms
- In cases who have a history of ocular surgery, follow-up should be performed based on the routine follow- up related to the type of the surgery
- In the event of any new signs or symptoms, short interval visits are recommended

Diagnostic procedures for all three forms

Light microscopy: Chronic inflammation, reduction of goblet cells, corneal thinning, progression of the conjunctiva to the cornea

Electron microscopy: Destruction of the basement membrane of corneal cells, vacuolization of cytoplasm (non-specific)

Fluorescent microscopy: Non-specific findings

Confocal microscopy: Corneal thinning, corneal epithelial irregularity, reduction of stromal keratocytes, spindle shape keratocytes, non-specific deposits in the cornea

Impression cytology: Limbal cell deficiency; however the degree of deficiency do not match with the clinical signs

Laboratory methods: None of the laboratory tests are specific for mustard gas exposure

MG, mustard gas