Evidence base for the efficacy of lid hygiene in the management of blepharitis

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Lid hygiene is the first line treatment for the management of blepharitis (lid margin disease) regardless of aetiology. Lid hygiene involves a process of cleaning the eyelid margins, using a variety of methods, to remove crusting/deposits from the lashes or occlusal surface of the lids, and also reduce the bacterial load associated with the condition. Lid cleansing is often combined with warm compresses (wet or dry) to loosen collarettes and crusts in anterior blepharitis and to melt meibum in posterior blepharitis.

The strongest evidence for the efficacy of any therapeutic intervention is obtained from 'randomised controlled trials' (RCTs) in which patients with the target condition are randomised to receive either the treatment under investigation or a comparator (e.g. placebo, no treatment or 'usual care'). For chronic conditions randomised cross-over trials with a suitable 'washout period', may also be an appropriate study design.

Ideally, neither the patient nor the treating clinician should be aware of which therapy was received. Although it is not always possible to mask the patient in a trial investigating the benefits of lid hygiene, the clinician assessing the outcome should be masked in order to reduce the potential for bias. When considering the evidence on lid hygiene, three questions arise:

1. Is lid hygiene effective in the management of blepharitis?
2. Of the available methods, is there any evidence for greater efficacy of one method compared to another?
3. Are there any adverse reactions associated with the various lid hygiene regimes?

Commonly used methods to clean the lid margins include:

- diluted baby shampoo (1:10) applied with a swab or cotton bud
- other home-made solutions, including sodium bicarbonate
- commercial products, e.g. dedicated lid-cleaning solutions or impregnated wipes

Recommendations for lid hygiene methods in current clinical guidance for eye care professionals (optometrists/ophthalmologists) and GPs, which are largely based on 'expert opinion' are provided in Appendix 1.

Is lid hygiene effective in the management of blepharitis?

A Cochrane Systematic Review on 'Interventions for chronic blepharitis', published in 2012, included three randomised and quasi-randomised studies that specifically evaluated lid hygiene interventions. The authors concluded that lid hygiene provides symptomatic relief for both anterior and posterior blepharitis, but they issued a call for more research to compare commercial products with conventional lid hygiene measures to determine relative effectiveness.

An extensive literature search was undertaken during the development of the Clinical Management Guideline on blepharitis (search date 18.6.18) and 13 studies evaluating the effectiveness of lid hygiene in blepharitis of various aetiologies were identified[2-15] (see Characteristics of Included Studies, Tables 2 and 3). Six of these studies used a RCT design (Table 2).[2-7]

The RCTs, which reported data on 274 participants, were conducted in Germany, Ireland, New Zealand, Paraguay and two in the USA. The clinical characteristics of the subjects were generally poorly described, but the majority were diagnosed with meibomian gland disease/lipid deficient dry eye. In four studies, a parallel group design compared different therapeutic interventions.[2-5] Two studies used a paired eye design; one of these compared baby shampoo to a dedicated lid cleanser[7]and another used an unspecified lid scrub for one eye and the fellow eye was used as an untreated control.[6]

Lid hygiene methods were varied, usually consisting of either neutral/baby shampoo or different proprietary lid wipes or eyelid-cleansing solutions, often combined with adjunct therapy such as warm compresses, lid massage or lubricating eye drops. The trials were of short duration (mean 5.7 weeks (SD 3.7)), and in most cases the reported outcomes were the effect of the interventions on symptoms and clinical signs of blepharitis (e.g. crusting, quality of meibomian gland secretion/gland plugging). [2,3,4,6,7] Three trials[3,6,7] evaluated tear break-time (TBUT) and one used conjunctival impression cytology to measure changes in gene expression of specific inflammatory markers and the goblet cell mucin MUC5AC.[7]

Compared to baseline, significant improvements were seen in symptoms and clinical signs for all interventions used.

We evaluated the overall quality of each study using the Cochrane Risk of Bias Tool as described in the Cochrane handbook.[16] Figures 1 and 2 present a summary of the risk of bias of included studies.

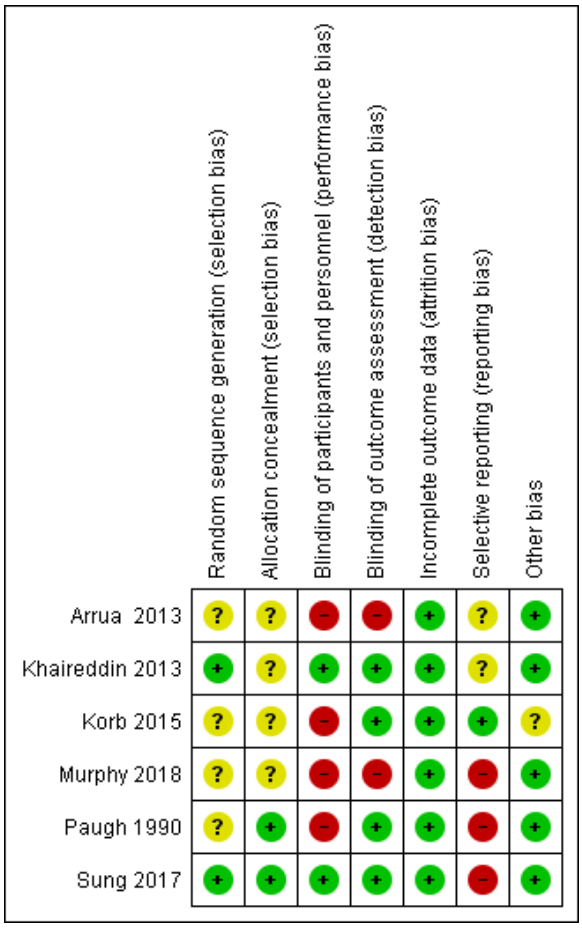

Figure 1. *Risk of bias: review authors' judgements about risk of bias for each included study. Green=low, Red=high, Yellow=unclear.*

Five of the six RCTs were judged to have a high risk of bias in at least one domain. Furthermore, for many domains, poor reporting meant that there was insufficient information to permit judgement of 'Low risk' or 'High risk' of bias. Only two studies[3,7] clearly described how the random sequence was generated and two studies[6,7] described how the allocation sequence was concealed. The nature of the interventions was such that masking of the participants was not always feasible, although in all but two studies outcome assessors were masked. We judged two studies[2,3] to have an unclear risk of selection bias, since no protocol or trial registry entry was available and it was therefore not possible to assess this domain. Three studies were at high risk of selective reporting bias. For one study, only participants who were compliant with lid hygiene were included in the analysis[6]; in another, the efficacy of lid hygiene was reported only for subjects who screened positive for demodex.[5] Although Sung et al 2017[7] registered their trial *a priori*, several of the reported outcomes were not pre-specified.

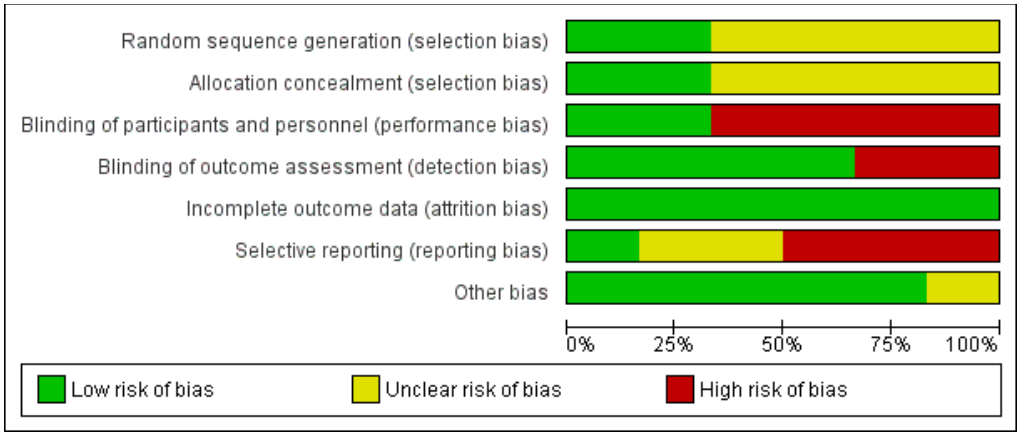

Figure 2. *Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.*

We also identified several non-randomised studies[8-15]. These were generally small interventional studies of short duration. In the comparative studies, no attempt was made to mask outcome assessors. These non-randomised trials were considered to be at a high risk of bias.

Of the available methods, is there any evidence for greater efficacy of one method compared to another?

Two RCTs compared lid hygiene with baby shampoo to commercially available products. Khaireddin et al 2013[3] compared a twice-daily application of dilute baby shampoo to a proprietary liposomal eyelid cleaner in 53 contact lens wearers with MGD. An improvement in signs and symptoms occurred relative to baseline in both treatment groups. However, the dedicated lid cleaning solution was statistically significantly more effective. The clinical significance of the observed differences in outcomes is unclear. Notably there was no difference in compliance or tolerability between the two regimes.

Sung et al 2017[7] conducted a double-masked, paired eye comparison between a dedicated eyelid cleanser applied to one eye and baby shampoo to the fellow eye in 43 participants with a clinical diagnosis of blepharitis. In terms of efficacy, both treatments were effective in reducing symptoms.

Twenty-three separate clinical signs involving the tears, the conjunctiva and eyelid margins were evaluated. Six of these (26%) showed a statistically significant improvement from baseline with the dedicated cleaner compared to four (17%) for the baby shampoo. Only the dedicated eyelid cleanser proved effective in reducing ocular surface inflammation (based on reduced expression of Matrix metalloproteinase 9 (MMP-9), a pro-inflammatory cytokine). A significantly higher proportion of participants preferred the eyelid cleanser to the diluted baby shampoo treatment (53% vs. 9%). Thirty eight percent of participants expressed no preference.

A non-randomised comparative study[11] recruited 26 patients, who were instructed to use a commercial lid scrub to their right eye and applied hypoallergenic soap to the left eye. The patients were followed for 4 months. In a subsequent study, 10 of the original patients continued using the commercial lid scrub on the right eye and switched to using dilute baby shampoo on the left. The study concluded that all methods of lid hygiene were effective in improving the slit-lamp signs and patient symptoms of blepharitis, although the sample size was too small to statistically compare the different regimes. There was a strong patient preference for the commercial lid scrub product, which the authors attributed to its 'ease and convenience of use'.

Are there any adverse reactions associated with the various lid hygiene regimes?

Only two studies provided data on adverse effects. None of the adverse events reported by Korb et al 2015[4] was considered to be treatment-related.

Sung et al[7] reported that MUC5AC expression decreased in eyes randomized to the baby shampoo treatment. MUC5AC is a secretory mucin produced by conjunctival goblet cells. The significance of this finding is unclear. The measurement of MUC5AC by conjunctival impression cytology is highly variable and there is considerable variation in goblet cell density within the normal bulbar conjunctiva. The 'significant reduction' in MUC5AC in this paired eye study was based on change from baseline for the eye treated with baby shampoo. However, the difference between the eyes at baseline and at day 28 was not significant.

Given that baby shampoo is commonly recommended by eye care professionals for lid hygiene, we identified only one case study of an adverse reaction to baby shampoo. Welling and co-workers[17] described a case of chronic eyelid dermatitis following the use of baby shampoo for daily lid scrubs. This was attributed to one of its constituents, cocamidopropyl betaine, which is a commonly used surfactant in cosmetic and personal care products.

Cost effectiveness

In addition to clinical effectiveness, another important consideration is the cost-effectiveness of treatment. We were unable to identify any studies that had conducted a formal cost-benefit analysis. Intuitively, it seems likely that the use of pre-prepared impregnated sterile pads would encourage compliance. However, these products are not available on an NHS prescription and therefore incur a cost to the patient. Wipes cost in the region of 20-36p each, and assuming one treatment per day (2 wipes) the cost of treatment for 1 year is in the range £146-£263 depending on

the particular product used. However, using a different area of the same wipe for the fellow eye (as recommended in the TFOS DEWS II lid hygiene video) would halve the treatment cost.

A typical price for Johnson's Baby Shampoo is £2.29 for 500ml. If 5ml is used per day the annual cost is less than £10 per year

Conclusions

It is important when making guideline recommendations that each recommendation is informed by the best available research evidence. The College of Optometrists Clinical Management Guidelines (CMGs) provide a reliable source of evidence-based information on the diagnosis and management of a number of eye conditions that present with varying frequency in primary and first-contact care. In the CMG for blepharitis, the following advice is provided for the non-pharmacological management of this condition:

Lid hygiene measures wipe away bacteria and deposits from lid margins, mechanically express the lid glands and lead to improved signs and symptoms in the majority of individuals. However, there is insufficient high quality evidence on the comparative efficacy of the various lid hygiene regimes. There is evidence that long-term compliance with lid hygiene measures may be poor.

The level of evidence was considered 'moderate' and the intervention was given a 'strong' recommendation (GRADE: Grading of Recommendations Assessment, Development and Evaluation).

There was insufficient evidence to make any recommendation based on the relative effectiveness of different methods of lid hygiene. Practitioners should therefore make patients aware of the options available e.g. the convenience of impregnated lid wipes versus the higher cost of these commercial products.

The CMGs are in a constant process of review, which allows appropriate new research evidence to be rapidly incorporated. There is a need for more high quality research comparing specific lid hygiene techniques to support future evidence-based recommendations regarding this simple and effective therapy. Although simple mechanical measures using lid hygiene and/or detergents have been shown to improve signs and symptoms in the great majority of participants and with no side effects, the studies assessing these measures have used different types of cleaning regime and comparison groups. Furthermore, the subjects in these studies were followed for a relatively short time. This is important since blepharitis is a chronic relapsing condition and compliance to lid hygiene measures may be an issue for long-term.[18]

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APPENDIX 1

Table 1. *Clinical guidance on lid hygiene methods for the management of blepharitis*

Clinical Guideline	Recommendation
American Academy of Ophthalmology. Preferred Practice Pattern Blepharitis 2013 https://www.aao.org/preferred-practice-pattern/blepharitis-ppp--2013	Cleaning the eyelid can be safely accomplished by having the patient gently rub the base of the eyelashes using either dilute baby shampoo or commercially available eyelid cleaner on a pad, cotton ball, cotton swab or clean finger tip
American Optical Association. Care of the patient with blepharitis. 2002 https://www.aoa.org/documents/optometrists/QRG-10A.pdf	Lid hygiene (e.g., warm, moist compresses, commercial lid scrub)
NICE Clinical Knowledge Summaries. Blepharitis 2015 https://cks.nice.org.uk/blepharitis	The eyelids should be cleaned in a stepwise manner twice daily initially, and then reduced to once daily as symptoms improve. Apply a warm compress to the closed eyelids for 5–10 minutes. Clean the eyelid by wetting a cloth or cotton bud with cleanser (for example, baby shampoo diluted 1:10 with warm water) and wiping along the lid margins. Eyelid scrubs or wipes can be used to clear away the scales on the lashes.
Moorfields Eye Hospital. Common eye conditions management 2015 https://www.moorfields.nhs.uk/content/gp-handbook	Lid hygiene: use a moistened cotton bud to gently clear the inside/back edge of your eyelids then firmly scrub off any flakes on the base of your eyelashes. This is best done in front of a mirror. The cotton bud may be moistened in tap water or you can make up a cleaning solution as below: • Add one teaspoon of baby shampoo to one cupful of previously boiled water, or • Add a ¼ teaspoon of sodium bicarbonate to a ½ a cupful of cooled boiled water. Mix thoroughly
TFOS- DEWS II Report 2017 http://www.tfosdewsreport.org/index.php?lng=en	In preference to using baby shampoo, there are now a wide variety of proprietary lid cleansing products available, which utilise a diversity of delivery mechanisms, including scrubs, foams, solutions, and wipes.

APPENDIX 2. Characteristics of included studies

Table 2. *Randomised Controlled Trials*

Study	Study design	Participants	Interventions	Outcomes
Arrua 2015[2]	Randomised open label parallel group design	45 subjects with chronic blepharitis	Group 1 (N=15): three times daily treatment with neutral shampoo applied with cotton swabs (3 times per day), warm compresses and lid massage Group 2 (N=15): lid hygiene (as group 1), warm compresses and lid massage and 0.75% metronidazole twice a day Group 3 (N=15): lid hygiene, warm compresses, lid massage and ointment containing 3.5% neomycin, 10% polymyxin and 0.5% dexamethasone three times a day Study duration: 2 months	Comparison with baseline: • change in symptoms • change in clinician grading of signs of blepharitis
Khaireddin 2013[3]	Randomised investigator masked parallel group design	53 contact lens wearers with anterior and/or posterior blepharitis	Group A (N=21): twice daily lid care (warm compresses (3 minutes), lid cleaning with with baby shampoo applied with cotton swabs, followed by lid massage) Group B (N=32) as above but lid hygiene using a commercially available lid cleaning solution Study duration: 4 weeks	Comparison with baseline: • change in symptoms • TBUT • clinician masked grading of slit lamp photos
Korb 2015[4]	Randomised investigator masked parallel group randomised controlled trial	26 subjects with MGD	Group 1 (N=13): Combination Treatment Group: lipid emulsion eye drops (4 times per day), omega 3 supplements and lid hygiene using commercial lid wipes (once daily). Group 2 (N=13): Warm Compresses Group: warm wet microfiber compress) to both	Between group comparison at 1m and 3m • difference in symptoms • difference in meibomian gland patency • Adverse effects

			eyelids for 8 minutes once daily Study duration: 3 months	
Murphy 2018[5]	Investigator-masked parallel group randomised controlled trial	86 subjects. 45 positive for Demodex Folliculorum (DF), 45 DF negative	Group A (N=28): Dr Organic Tea Tree Face Wash Group B (N=30): Nightly treatment with commercial lid wipes Group C (N=28): in house lid scrub with Blephex followed by nightly treatment with lid wipes Study duration: 4 weeks	Between group comparison at 2 weeks and 4 weeks: • difference in symptoms • difference in DF count Results presented for DF +ve subjects only
Paugh 1990[6]	Investigator-masked randomised intra-individual comparative study	21 contact lens wearing subjects with MGD	Daily regime of warm compresses and lid scrubs twice daily to a randomly selected eye. The fellow eye was untreated Study duration: 2 weeks	Comparison with baseline: • change in symptom score • TBUT • Gland expression
Sung 2018[7]	Double-masked randomised intra-individual comparative study	43 subjects with a clinical diagnoses of blepharitis	Lid hygiene performed twice a day using a commercial eyelid cleanser applied to the eyelids of one eye (randomized) and diluted baby shampoo (1:10 dilution) to the fellow eye. Study duration: 4 weeks	Comparison with baseline: • change in symptom score • change in tear film evaluation (including TBUT) and ocular signs of blepharitis • change in expression of MMP-9 and MUC5AC

Table 3. *Non-randomised trials*

Study	Study design	Participants	Interventions	Outcomes
Doan 2012[8]	Open label prospective interventional study	33 subjects with self-declared blepharitis/ sensitive skin or eyes	Lid hygiene with commercially available aqueous gel (applied on nonsterile, nonwoven compresses) Duration: 3 weeks	Comparison with baseline: • change in TBUT • participant views of product acceptability
Key 1996[9]	Open-label non-randomised intra-individual comparative study	26 subjects with chronic blepharitis (20/26 contact lens wearers)	Lid hygiene with commercially available cleaning pads to the right eye (morning and evening) and hypoallergenic soap to the left (applied with a clean fingertip for one minute) for 4 months. Baby shampoo (N = 10) compared to commercial lid wipes: as part of a 3 month study extension, 10 participants replaced Neutrogena lid scrubs in the left eye with diluted baby shampoo (50:50 dilution) Duration 4 months	Comparison with baseline • change in symptoms • change in clinical signs • subject rankings of effectiveness and ease of use
Kobayashi 2016[12]	Open label prospective interventional study	10 subjects with MGD 10 normal controls	Eyelid hygiene with specially formulated 'eyelid shampoo', applied using a cotton swap or fingertip and massaged into the eyelashes twice a day Duration 2 months	Comparison with baseline • change in symptoms • change in clinical signs
Lee 2017[13]	Open label prospective interventional study	32 subjects with moderate to severe MGD	Mechanical expression of MG by clinician using 'meibomian gland squeezing forceps' once per week. Lid cleaning with commercially available cleaner with warm compresses twice per day	Comparison with baseline • change in TBUT • change in clinical signs

			Duration: 1 month	
Ngo 2017[14]	Open label prospective interventional study	28 participants with dry eye signs and symptoms (including MGD)	Lubricating eye drops 2-4 X per day, commercially available eyelid wipes 1-2x per day and omega 3 supplements Duration: 3 months	Comparison with baseline • change in symptoms • change in clinical signs
Guillon 2012a[9], 2012b[10]	Prospective interventional comparison study	40 subjects with anterior blepharitis or MGD (12/40 contact lens wearers)	Eyelid hygiene with commercially-available wipes twice a day for 3-weeks and then once a day for 3 months Duration: 3 weeks	• Meibomian gland expression • clinician grading of lid margins change in symptoms
Romero 2004[15]	Prospective interventional comparison study.	37 subjects with a clinical diagnosis of MGD	Warm saline lid soaks (one teaspoon in 1 litre of water) applied to closed eyelids with cotton balls followed by cleaning the lashes with a cotton-tipped applicator. Regime conducted 4 times per day for 2 weeks and then twice a day for 4 weeks	Comparison with baseline • change in symptoms • TBUT • clinician masked grading of slit lamp photos