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Ophthalmology

ALLERGIC CONJUNCTIVITIS: A PRACTICE PATTERN SURVEY FROM NORTH INDIA

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ABSTRACT PURPOSE: The purpose of this survey was to establish the prevalence of AC and to know the practice pattern of managing ocular allergy in north India.

METHODS: A descriptive cross sectional study done in the states of north India, involving registered practicing ophthalmologists (RP). The survey was conducted in the month of May 2019. 14 fourteen survey questionnaire prepared on significant clinical situations related to ocular allergy was sent via goggle form to 300 Ophthalmologists of north India. The response was recorded and analyzed.

RESULTS: The survey was participated by 232 RP (77.33%) out of 300 whom the questionnaire was sent. The results analysis involved epidemiological, treatment and complication pattern.

CONCLUSION: AC patients form a significant proportion of our clinical patients specially in summer season. The chronic nature of this disease specially VKC needs a judicious use of different pharmacological agents considering their adverse effects. Newer molecules like Alcaftadine, Bepotastine and various Immunomodulators need further study by randomized clinical trials for their relative efficacy as survey are not sufficient to give us a clear indication towards rationalized use.

KEYWORDS: Allergic Conjunctivitis, Vernal Kerato Conjunctivitis, Immunomodulators

Ocular allergy is one of the most common prevailing clinical conditions but is often underdiagnosed and undertreated. It encompasses a group of inflammatory response of eye affecting the ocular surface. The clinical presentation is usually in the form of irritation, redness, itching and watering. There are various clinical forms of ocular allergies- seasonal allergic conjunctivitis (SAC), perennial AC, vernal kerato conjunctivitis (VKC) and atopic kerato conjunctivtis(AKC). The recent understanding of inflammatory cells, mediators, and immunologic events related to ocular allergy has led to development of newer diagnostic and therapeutic means for it.

The purpose of this survey was to establish the prevalence of AC and to know the practice pattern of managing ocular allergy in north India. To know the established utility, usefulness and efficacy of various pharmacological agents, both recent and proven ones, was another goal of this survey.

METHODS

It is a descriptive cross sectional study done in the states of north India, involving registered practicing ophthalmologists (RP). The survey was conducted in the month of May 2019. Survey questionnai reprepared on significant clinical situations related to ocular allergy was prepared after literature search and was sent via goggle form to 300Ophthalmologists.In this survey disease severity and nature of disease in terms of chronicity has been defined as per the guidelines given by Gokhale N. The preamble of questionnaire has this classification.

- Mild disease Symptomatic (redness and itching) patient with congestion and fine velvety papillae but no corneal involvement.
- Moderate disease-Corneal involvement in the form of fine punctate erosions, Horner-Trantas dots and focal limbalinflammation and thickening of <6 clock hours.
- Severe disease Large active cobblestones papillae, coarse erosions or keratitis, macroerosions, and severe limbal inflammation >6 clock hours.
- Intermittent disease –Inflammation free intervals of >2-3 months during which the patient is off medications.
- Chronic VKC Inflammation free intervals of <1 month during which the patient is off medications.

The questionnaire included as mentioned in table 1. The survey was initially checked by the co investigators. Google form based survey results were collected and converted to excel form and analyzed.

(Table 1)

RESULTS AND DISCUSSION

The survey was participated by 232RP (77.33%) out of 300 whom the questionnaire was sent.

What percentage of your OPD patients are suffering from some variant of AC

According to our survey in summer season 43.54% of RP have reported that the prevalence of AC is more than 30% of their total OPD patient volume. 35.89% RP reported it between 20-30% and 19.23% have reported it to be less than 10% of their OPD volume.

Whereas in other seasons, majority of RP (52.17%) have reported that the AC patients form less than 10% of their OPD volume, 34.78 % stated it between 10-20% and 13.04% between 20-30%. None of the RP has reported it to be more than 30% in other seasons. This shows a wide seasonal variation in overall prevalence of AC.

When we did our literature search it was found that the epidemiological profile of allergic conjunctivitis has not been clearly defined due to lack of consensus over its strict definition and diagnostic criteria. Depending upon geographical region and the age group of population under study ocular allergy affects around 5-22% of population.² A large cross sectional study from Asia Allergies in Asia Pacific Study (AIAP) conducted across nine countries screening 33,378 households reported that ocular symptoms were present in 20-30% in most of East and southeast Asia, whereas this was significantly higher with up to 56–60% in Australia likely to have been contributed by seasonal allergies.3Anothercross-sectional survey conducted in a semiurban low-income community in Chandigarh, India among children of age group 5-15 years has reported the prevalence of allergic conjunctivitis was 12.22%. ⁴. The role of allergens and seasonal variation of allergic conjunctivitis has been well documented in literature. 5,6 The seasonal variation in prevalence of AC is related to its immunopathology. SAC is usually caused by airborne allergens and is more common in summer and spring season with symptoms disappearing in winter season. On the other hand, PAC presents in chronic form with seasonal exacerbation. Malu N.K has reported the overall prevalence of AC around 32%, starting to rise from May, and peaking in July, then declining thereafter and reaching the lowest level in December.

Majority (more than 50%) of your AC patient belong to which age group

In our survey, 62.02% of RP have reported that their majority of AC patient belong to less than 10 year age group, 29.11% in the 10-20 year age group, 6.32% in the 20-30year age group and only 2.53% RP have reported that the majority of AC patient belong to >30 year of age group.

Various studies have reported AC as mainly a disease of younger population. Malu N.K has reported that AC is significantly more prevalent in the younger age group, showing a prevalence of 38.4% in those aged 0-16 years and least in the age group above 50 years

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(4.9%). Baab et al has reported that in most cases, onset occurs in patients younger than 20 years old with decreasing prevalence in older populations.

What percentage of your AC patients belong to vernal keratoconjunctivits group

In our survey, 21.51% of RP responded by stating that less than 20% of their patients suffered from VKC, Majority of RP(46.83%) had 20-40% of VKC patients among AC ,where as 20.25% of RP have reported it to be between 40-60% , 10.12% between 60-80% and 1.26% as more than 80% of their AC patients have suffering from VKC

VKC is a subgroup of AC, more prevalent in tropical countries. A large prospective study involving 1079 patients of ocular allergy has reported that SAC, PAC, AKC and VKC accounts for 81.2%, 10.6%, 4.4% and 3.8% of total cases of AC respectively. In another study based on 134 patients of AC, Belfort et al reported that VKC forms 46% of total cases of AC.

Common presenting symptoms of a patient of AC in decreasing order of frequency

In our survey also, Itching was the most common presenting symptom reported by 64.10% of RP, followed by redness (15.38%), irritation (14.10%) and watering (5.12%). Ocular redness, itching, irritation, watering are the usual symptoms associated with AC. Usually these symptoms are well tolerated but can be debilitating too. Different studies have reported itching as the most common symptom 10,11 with incidence ranging from 41% 15 to 88% 13

Do you advise any systemic/ophthalmic investigation in patients of $\mathbf{A}\mathbf{C}$

In our survey clinical evaluation of dry eye was the most commonly performed investigation. Dry eye evaluation alone or in combination with other investigations was performed by majority (76.47%) of RP. 32.35% RP evaluate serum IgE , 19.17% keratometry and 7.35% RP evaluated the patient for corneal topography.

AC often co-exists with systemic (allergic rhinitis, asthma and eczema) and ocular pathologies and the diagnostic investigations highlight the type of hypersensitivity reaction and ocular co-pathologies which can affect the treatment protocol. Although IgE plays an important in pathogenesis,total serum IgE is no longer considered indispensable for diagnosis of AC as the normal values do not exclude the diagnosis. Conjunctival cytodiagnosis, conjunctival provocation test, tear specific IgE assay can be of diagnostic as well as of therapeutic value. ¹⁴Among ocular pathologies, dry eye, Keratoconus, refractive error are known associates of AC. A study based on 689 patients of various symptoms of ocular allergy has reported that most patients with "itchy eyes" consistent with AC also have dry eyes. ¹⁵

What is your preferred line of treatment for a patient of recent onset AC

The clinical staging of AC is based on symptoms and signs and multiple treatment algorithms have been proposed based on severity of disease. In this survey disease severity has been defined as per the guidelines given by Gokhale N. According to our survey, the preferred treatment for different stages of disease is as follows .All respondents were using combination of medications.

Mild AC – Majority of RP use tear substitute (70.51%), Antihistamine +mast cell stabilizers (58.97%) and topical antihistaminic eye drops (26.92%). Topical vasoconstrictors are used by 16.66%, Topical NSAID and steroid both by 8.97% of RP and systemic antiallergics by 3.84%. Immunomodulators are prescribed by only 1.28% of RP.

Moderate AC – For moderate AC, mast cell stabilizer (78.37% of RP), topical steroid (74.32% of RP) and tear substitute (68.91% of RP) form a major part in prescription. Topical Immunomodulators and systemic antiallergics are prescribed by 24.32% and 20.27% of RP respectively. Topical antihistaminic (16.21% of RP), NSAID (13.51% of RP) and vasoconstrictors (12.16% of RP) are of lesser preference for treating these cases.

Severe AC – Topical steroids (86.15% of RP), immunomodulator (75.38% of RP), tear substitute (72.30% of RP) and mast cell stabilizer (64.61% of RP) are the preferred treatment by most of the RP. Systemic

antiallergics are prescribed by 29.23% of RP. Topical NSAID (10.76% of RP), vasoconstriction (9.23% of RP) and topical antihistamine (9.23% of RP) do not have a significant place in prescriptions.

Reference - Table 2 - Part I

For a case of chronic/recurrent AC, your preferred line of treatment

Chronic variant of VKC is not uncommon and one of the largest study on VKC patients from India has reported that 36% of patients of VKC have chronic perennial disease. For cases of chronic AC avoidance of allergens, lubricants, antihistaminic + mast cell stabilizers+ low frequency loteprednol, 0.5% cyclosporine, systemic antiallergicdrugs(when ocular symptoms are associated with other allergic comobidities) have been recommended. 1,14

In our survey majority of RP treat cases of recurrent AC with use of mast cell stabilizers (79.74%), along with a combination of tear substitute (71.42%) or topical steroid (61.90%) or Immunomodulators (69.84%). Topical NSAID and Systemic antiallergic are prescribed by 11.39% and 24.05% RP respectively. Vasoconstrictors was used by only 3.7% of RP.

Opinion about newer mast cell stabilizers like Alcaftadine and Bepotastin, their place in practice and superiority over Olopatadine

In our survey, 17.94% of RP still do not prescribe either of these two newer molecules. Among the practitioners prescribing these two46.15% prescribe both of these molecules, 32.05% only Bepotastine and 3.84% only Alcaftadine for treatment of AC.

Among theBepotastin prescribing ophthalmologists, 40.98% found it to be as effective as Olopatadine, 24.59% found it more effective, 22.95% as less efficient and 11.47% were not sure about their efficacy. Ophthalmologists prescribing Alcaftadine, 43.58% found it to be equally effective as Olopatadine, 23.07% found it more effective, 30.76% as less effective and 2.56% were not sure about its efficiency..

The new generation of antiallergic + mast cell stabilizerslike Alcaftadine / Bepotastin has been well accepted but their efficacy and supremacy over each other and over Olopatadine is a subject of research. Study by McLaurin EB based on conjunctival allergen challenge (CAC) over 284 subjects has suggested that once-daily Alcaftadine 0.25% ophthalmic solution demonstrated greater efficacy in prevention of ocular itching compared with Olopatadine 0.2% at 3 min post-CAC (primary endpoint) and over all time points, 16 h post-treatment instillation.¹⁶

Another study based on patients' preference of medication comparing therapeutic performance of Bepotastine besilate 1.5% ophthalmic solution and Olopatadine hydrochloride 0.2% ophthalmic solution has reported that patients preferred Bepotastine besilate 1.5% over Olopatadine hydrochloride 0.2% by two-to-one for the treatment of allergic conjunctivitis.¹⁷.

One of the recent study comparing all three molecules in patients of allergic conjunctivitis has reported similar efficacy of three medications in relieving symptoms and inefficacy in regressing palpebral and limbal papillae in cases of allergic conjunctivitis. ¹⁸

Topical steroid of choice in cases of mild, moderate and severe AC In our survey we found the following pattern of topical corticosteroid use in AC-

Mild AC – Among the steroid users for mild ACLotepred nol(64.38%)Fluoromethanol(32.87%) was used by RP. Topical Dexamethasone and Prednisolone are used equally, only by 1.36% of RP

Moderate AC - The topical steroid of choice for 62.02% of RP was Loteprednol, 26.58% RP usedFluoromethanol. Dexamethasone was preferred by 6.32%, Prednisolone by 5.06% and Betamethasone by 2.53% of RP.

Severe AC – Topical Prednisolone (34.17%), Loteprednol (31.64%), Dexamethasone (18.98%) are the three most common agents used for treating severe AC as per the survey response. The next two pharmacological agents are Fluoromethanol (12.65%) and

Betamethasone (3.79%).

Reference-Table 2-Part II

Corticosteroids -cytosolic glucocorticoid receptors complexes act at genomic level by decreasing the production of several inflammatory cytokines. This leads to inhibition of cell infiltration, stabilization of intra and extra cellular membranes, blocking of A2 phospholipase and increased production of histaminase and decreased production of histamine. Despite having a strong antiallergic properties, ocular corticosteroids are not considered first-choice therapy for AC. Although less potent drugthe so-called soft corticosteroids (eg, Fluorometholone, Medrysone, Loteprednol and Rimexolone) are used to treat moderate inflammation. When inflammation is severe, the drugs of choice are Betamethasone, Dexamethasone, and prednisolone. Loteprednol etabonate (0.2%) is currently the only ophthalmic corticosteroid specifically developed for and approved by the Food and Drug Administration for treatment of SAC.

Duration of topical steroid usually you advise for

The next survey question was about the duration of steroid use in different grade of AC. In our survey

Mild AC – Among the steroid users, 77.58% RP uses topical steroid for a period <2 weeks, 18.96% for a period of 2-4 weeks and 3.44% for a duration of 4-6 weeks. None of respondents uses steroid for more than 6 weeks in mild cases.

Moderate Ac - 62.85% of RP uses steroid eye drop for a period of 2-4 weeks, 21.43% for a period of less than 2 weeks. 14.28% for 4-6 weeks and 1.4% for a period more than 6 weeks.

Severe AC – Nearly 50% (47.22%) RP uses topical steroid for a period of 4-6 weeks, 33.33% for a period of 2-4 weeks, 11.11% for less than 2 weeks and 8.33% for a period more than 6 weeks.

Reference - Table 2 - Part III

Use of corticosteroid is associated with multiple sight threatening complications like development of cataract, glaucoma, chances of secondary infection etc. In cases of AC, judicious use of corticosteroid has been recommended example in chronic form of unwieldy conjunctivitis and acute form of selected cases. ⁹Corticosteroids are appropriate for short courses (up to 2 weeks); however, if needed for longer durations, an eye examination should be carried out, including baseline assessment of cataracts and intraocular pressure measurement.²²

Do you use topical Immunomodulators? Preferred Immunomodulators

The next survey question was about use of different Immuno modulators and its percentage.

According to our survey Immunomodulators are not used for treatment of AC by only 3.79% of RP. 76.31% of RP are using topical Tacrolimus ointment in different strength (0.03% Tacrolimus by 86.20%, 0.1% Tacrolimus by 13.79%). 5.17% RP are using both strength of Tacrolimus. Among the Cyclosporin users topical Cyclosporin drop is used by 52.63% of RP .Out of which 75% of them use 0.05% strength and 25% of practiotner use 0.1% Cyclosporin eye drop.

Immunomodulators have been widely accepted for their role in AC as steroid sparing agents. Their effect is mainly due to inhibition of T-cell activation. As a result, a distinct and main pro inflammatory cytokine signature is not expressed, including interleukins. The immunopathology of chronic diseases, such as VKC and AKC, involves predominantly T lymphocytes, and therefore the agents that inhibit T-cell activation seem to be the appropriate treatment for chronic allergic eye diseases. Topical Cyclosporin and Tacrolimus are the two commonly used Immunomodulators in clinical practice. The efficacy of 0.05% and 0.1% topical Cyclosporinhas been very well documented in clinical studies.^{23,24} In one of the study comparing efficacy of 0.1% dexamethasone and 2% cyclosporine on 366 patients of VKC reported both of them to be equally effective in relieving sign and symptoms of disease but compliance to cyclosporine due to stinging was poor incomparison to 0.1% Dexamethasone.²⁵0.03% Tacrolimus ointment with once-daily treatment, is effective, well tolerated, and safe in the treatment of severe atopic eyelid disease,

VKC and AKC patients.²⁶Another prospective study involving 36 patients of AC has reported 0.1% Tacrolimus in twice daily dose to be an effective treatment.²⁷

Duration for which you prescribe Immunomodulators

In our survey 44.59% of Immunomodulators user has reported to use it for a period more than 12 weeks, 31.08% for 4-8 weeks, 20.27% for a period of 2-4 weeks and only 5.40% users for a period of less than 2 weeks.

Clinical studies have suggested that prolong use of Immunom odulators are not associated with any significant ocular and systemic side effects. A long term study evaluating effect of 0.1% Tacrolimus has reported it to be well tolerated and safe over a period of 48 months. **Another study involving 156 children with VKC treated with topical cyclosporine eye drops 1% and 2% over a period ranging from two to seven years [mean time 3.8 +/- 1.09 years] has concluded that topical cyclosporine is easily handled even by children, with safe and effective results even when it is used over a long period of time. **

Association of mobile and other digital devices and AC

In our survey, 37.97% of RP were either not sure (18.98%) or did not find any association between AC and digital device usages. RP reporting association between these two (62.02%) have a wide variation in their responses. On one hand few of them have reported it as low as 5% and few reporting it as high as 80%.

Moon JH et al reported use of smart phone and other video display devices as an important factor for rising prevalence of dry eye. ³⁰Although dry eye disorder is more prevalent in cases of ocular allergy ³¹. However the direct role of digital devices as a causative of AC has not been reported.

Prevalence of complication of AC (Disease + treatment relate)

Our last survey question was about various complication associated directly or indirectly to AC. We received following responses

Shield's ulcer -11.39% of RP were not sure about its prevalence. Those reporting it 91.42% of them reported it to be less than 10%, 8.15% reported it between 10-20%.

Keratoconus – 30.37% of RP were not sure about its prevalence in AC. Among the positive reports, 90.90% reported it to be less than 10% and 9.09% between 10-20%.

Corneal scar -26.58% RP were not sure about the prevalence of corneal scar in AC. Those who reported positively 75.86% reported it to be less than 10%, 22.41% between 10-20% and 1.75% between 20-30%.

Steroid induced glaucoma – 16.45% of RP were not sure about its prevalence. 72.72% of ophthalmologists reported it having less than 10% prevalence, 24.24% between 10-20% and 3.03% between 20-30%.

Steroid induced cataract -20.25% of RP were not sure about its prevalence. Among the positively reporting participants, 77.77% reported it to be less than 10%, 17.46% between 10-20% and 4.76% between 20-30%.

Chronic AC especially VKC and AKC is associated with multiple ocular complication, both disease and treatment related. AC and the pharmacological agents used for its treatment; specially corticosteroid has been known to cause multiple ocular complications. Clinical trials have demonstrated C-20 ester corticosteroid to have similar efficacy to C-20 ketone corticosteroids in the prevention or treatment of the signs and symptoms of SAC but with a greatly improved safety profile both in term of IOP rise and cataract formation. In one of the important epidemiological study from India, based on demographic and clinical profile of VKC, has reported corneal scarring as the most common complication(11%) followed by peripheral neovascularization(7%), keratoconus(6%), steroid induced cataract(4%) and glaucoma(3%) and shield ulcer(3%). Bonini et al have reported reduced visual acuity in 6% of cases of VKC due to corneal scarring, 9.7% incidence of shield ulcer and steroid induced glaucoma in 2% of cases.

CONCLUSION

AC patients form a significant proportion of our clinical patients

specially in summer season. The chronic nature of this disease specially VKC needs a judicious use of different pharmacological agents considering their adverse effects. Newer molecules like Alcaftadine, Bepotastine and various Immunomodulators need further study by randomized clinical trials for their relative efficacy as survey could not give us a clear indication towards rationalized use. Similarly the role of mobile and other digital devices as causative agent of AC needs to be evaluated. Different ocular complications related to AC should be closely looked for in clinical practice.

FINANCIAL SUPPORT AND SPONSORSHIP

CONFLICTOFINTEREST

None

Table 1: Allergic conjunctivitis practice pattern: Survey questions

Kindly select your response

What percentage of your OPD patients are suffering from some variant of AC-

Summer Other seasons <10% 10-20% 20-30% >30%

2. Majority (>50%) of your AC patients belong to which age group-

<10vr

10-20yr

20-30yr

>30yr

What percentage of your allergic conjunctivitis patients belong to vernal keratoconjunctivitis group -

<20%

20-40%

40-60%

60-80%

>80%

- Please arrange these presenting symptoms of AC, in decreasing frequency - 1 -redness, 2- watering, 3 - itching, 4 - ocular irritation - Example 3,2,1,4
- 5. Do you advise any systemic/ophthalmic investigation in these patients -

Dry eye evaluation

Keratometry

Topography

Serum Ig E level

What is your preferred line of treatment for a patient of recent onsetAC -

Severe

Moderate

Topical vasoconstrictors

Antihistaminic

Antihistaminic +Mast cell stabilizer

Topical NSAIDs Topical steroid Tear substitutes Immunomodulators

Systemic antiallergics

For a case of chronic / recurrent AC, your preferred line of treatment -

Topical vasoconstrictors

Antihistaminic

Antihistaminic +Mast cell stabilizer

Topical NSAIDs

Topical steroid

Tear substitutes

Immunomodulators Systemic antiallergics

Other(please specify)-

What is your opinion about newer mast cell stabilizers like Alcaftadine, Bepotastine - Their place in your practice, superiority over Olopatadine -

Do not prescribe

Prescribe Bepotastine

Prescribe Alcaftadine

Equal efficacy as Olopatadine

Less efficient than Olopatadine

More efficient than Olopatadine

Topical steroid of choice in cases of mild, moderate and severe AC Mild Moderate

Dexamethasone

Prednisolone acetate

Loteprednol

Fluoromethalone

Betamethasone

10. Duration of topical steroid usually you advise for -

Mild Moderate

Severe

<2 week

2-4 week

4-6 week

>6 week

11. Do you use immunomodulators like Tacrolimus, Cyclosporine for AC.

Tacrolimus(0.03%)

Tacrolimus(0.1%)

Cyclosporine (0.05%)

Cyclosporine(0.1%)

12. Duration for which you prescribe immunomodulators –

<2 week

2-4 week

4-8 week

>12 week

- 13. How often you see association of excessive mobile or other digital devices use with AC -
- 14. In what percentage of cases you see -
- Disease related complications like shield's ulcer, keratoconus, corneal scarring
 - Treatment related complication-glaucoma, cataract

<10% 10-20% 20-30% >30%

Shield's ulcer Keratoconus

Corneal scar

Steroid induced glaucoma Steroid induced cataract

Table 2 – Part I – Question no 6				
	Mild AC/Percentage of RP	Moderate AC/ Percentage of RP	Severe AC / Percentage of RP using for	
	using for treatment	using for treatment	treatment	
Topical Vasoconstrictors	16.66%	12.61%	9.23%	
Topical antihistaminics	26.92%	16.21%	9.23%	
Mast cell stabilizer +antihistaminic	58.97%	78.37%	64.61%	
Topical NSAID	8.97%	13.51%	10.76%	
Topical steroid	8.97%	74.32%	86.15%	
Tear substitute	70.51%	68.91%	72.30%	
Topical Immunomodulators	1.28%	24.32%	75.38%	
Systemic antiallergic	3.84%	20.27%	29.23%	
Table 2 – Part II – Ouestion no 9				

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Topical Steroid of choice/ Among the steroid users	Loteprednol - 64.38% Fluoromethanol - 32.87% Dexamethasone - 1.36% Prednisolone - 1.36%	Loteprednol - 62.02% Fluoromethanol - 26.58% Dexamethasone - 6.32% Prednisolone - 5.06% Betamethasone - 2.53%	Prednisolone - 34.17% Loteprednol - 31.64% Dexamethasone - 18.98% Fluoromethanol - 12.65% Betamethasone -3.79%
Table 2 – Part III – Question no 10			
Duration of topical steroid use	period <2 weeks - 77.58% 2-4 weeks - 18.96% 4-6 weeks - 3.44%	period < 2 weeks -21.43% 2-4 weeks - 62.85% 4-6 weeks - 14.28% >6 weeks - 1.4%	period < 2 weeks - 11.11% 2-4 weeks - 33.33% 4-6 weeks - 47.22% > 6 weeks - 8.33%

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