

Key Publications For The Cow's Milk-related Symptom Score

CoMiSSTM



INTRODUCTION

CHALLENGES IN CMA DIAGNOSIS AND LOW AWARENESS

Cow's Milk Allergy (CMA) is one of the most common food allergies in early life, affecting up to 3% of infants globally. However, diagnosing it can be challenging as it can take months and multiple visits to get an official diagnosis. ²

Awareness of CMA symptoms can be low and misunderstood, especially in primary care, leading to either under or overdiagnosis, both having consequences for infants, parents and caregivers and the health care system.^{3,4}

CHALLENGES CONSEQUENCES Increase costs and higher Symptoms can overlap healthcare usage^{3,4} with other common infant conditions.¹ Many primary care Inappropriate dietary changes³ HCPs are not always very familiar with the common symptoms of CMA and the guidelines for diagnosis Lower quality of life^{5,6} and management.²

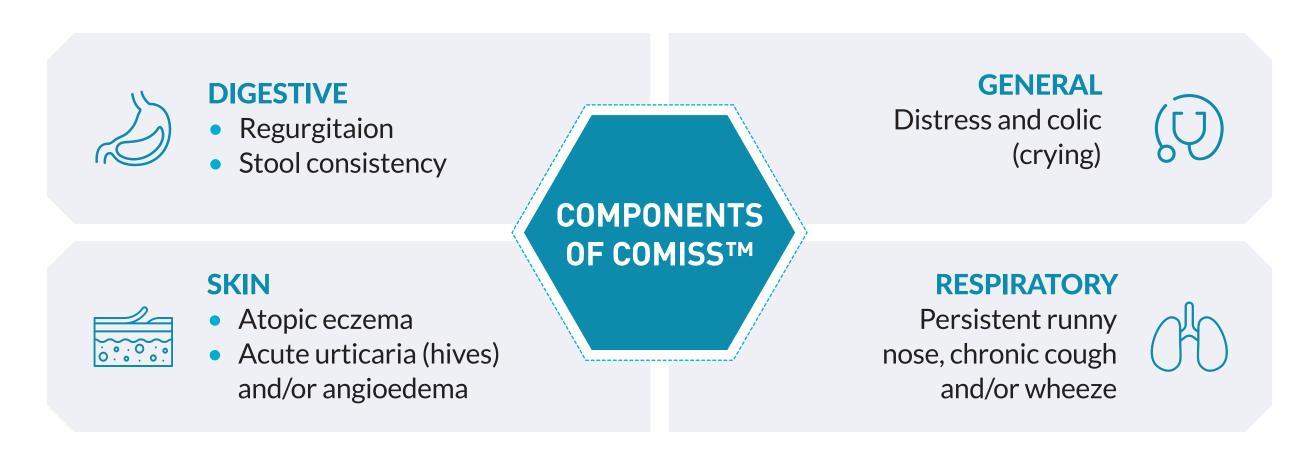
WHAT IS COMISS™ AND HOW IS IT USED?

CoMiSS[™] is a Cow's Milk-related Symptom Score developed by international experts in 2015.¹ Since 2015, >25 clinical studies and publications using CoMiSS[™] endorse its use as an awareness tool for the early identification of CMA.³



CoMiSS™ helps increase awareness of the most common symptoms associated with CMA supporting earlier diagnosis

CoMiSSTM quantifies and scores the number and severity of symptoms seen in infants with suspected CMA. When the score is \geq 10, CMA is suggested, while a score <6 is unlikely to be CMA, and other causes should be investigated.¹



CoMiSS[™] was updated in 2022 with minor clinical changes and the addition of statements to improve its functionality in clinical practice. It remains a simple to use, easy, fast and non-invasive awareness tool.¹

1. Vandenplas Y, et al. Nutrients. 2022;14(13):2682. 2. Lozinsky A, et al. Children. 2015;2:317-329. 3. Bajerova K, et al. Nutrients. 2022;14(10):2059. 4. Lifschitz, et al. Eur J Pediatr. 2015:174, 141-150. 5. Meyer R, et al. World Allergy Organ J. 2017; 10(1):8. 6. Sorensen K, et al. Immun Inflamm Dis. 2022; 10(3):e572





COMISSTM CLINICAL EVIDENCE

1.

COMISS™ KEY PUBLICATIONS BETWEEN 2014 AND 2021

- 2015: A Workshop Report on The Development of The Cow's Milk-Related Symptom Score Awareness Tool for Young Children
- 2018: The Cow Milk Symptom Score (Comiss™) in Presumed Healthy Infants
- 2019: Testing The Cow's Milk-Related Symptom Score (Comiss™) for The Response to a Cow's Milk-Free Diet in Infants: A Prospective Study
- 2020: The Cow's Milk-Related Symptom Score (Comiss™): Healthcare Professional and Parent And Day-to-day Variability
- 2021: How Are Infants Suspected to Have Cow's Milk Allergy Managed? A Real World Study Report

2.

COMISS™ KEY PUBLICATIONS FOR UPDATED TOOL FROM 2022

- 2022: The Cow's Milk-Related Symptom Score: The 2022 Update
- 2022: The Cow's Milk-Related Symptom Score (Comiss™): A Useful Awareness Tool
- 2022: Assessment of The Cow's Milk-Related Symptom Score (Comiss™) as a Diagnostic Tool for Cow's Milk Protein Allergy: A Prospective, Multicentre Study in China (Mosaic Study)
- 2023: Cow's Milk-Related Symptom Score (Comiss™): From Bristol to Brussels Stool Scale
- 2024: Cow's Milk-Related Symptom Score (ComissTM) Values in Presumed Healthy European Infants Aged 6-12 Months: A Cross-Sectional Study





A WORKSHOP REPORT ON THE DEVELOPMENT OF THE COW'S MILK-RELATED SYMPTOM SCORE AWARENESS TOOL FOR YOUNG CHILDREN

Yvan Vandenplas et al. Acta Pædiatrica. 2015;104(4):334-339.



Study objectives

To reach a consensus among International Experts experienced in managing children with gastrointestinal problems and/or atopic diseases to adapt the existing symptom-based score (SBS) into a cognitive tool for recognizing milk-related symptoms in young children.



Subjects and methods

A group of International Experts conducted a workshop in 2014 to develop the first version of CoMiSSTM. They clandestinely voted on questions about SBS based on published data from several pilot trials. They voted using a nine-point scale, ranging from one for strongly disagree to nine for fully agree.



Endpoints

More than 80% of the voters had to score six or above to reach an agreement



Results

All of the SBS aspects were reached in consensus:

- SBS can serve as a new awareness tool for assessing symptoms related to cow's milk
- Healthcare professionals benefit from the SBS as a quick and easy-to-use tool for identifying cow's milk-related symptoms.
- While SBS cannot serve as a diagnostic tool for CMPA, it does, however, signal symptoms associated with cow's milk consumption
- Substitute the term SBS with Cow's Milk-related Symptom Score awareness tool (CoMiSS™)

CoMissTM

offers primary care clinicians
a simple, fast, and easy-to-use
tool to recognize symptoms
associated with
cow's milk

SUMMARY OF CONSENSUS

- CoMiSS™ awareness tool is not a diagnostic test for CMA.
- CoMiSS[™] can be used as a useful awareness tool for cow's milk related symptoms.
- Primary HCP would benefit from a rapid and easy-to-use awareness tool for cow's milk related symptoms.

This report published the development of the first version of CoMiSS™





THE COW MILK SYMPTOM SCORE (COMISSTM) IN PRESUMED HEALTHY INFANTS

Vandenplas Y et al. PLoS One. 2018 Jul 18;13(7):e0200603.



Study objectives

To determine an age-related CoMiSSTM in healthy infants to reduce the risk of false reassurance in negative results or over-diagnosis of CMPA in positive results.



Subjects and methods

An international multicenter cross-sectional study involved healthy infants aged ≤6 months.

Age-related CoMiSS™ symptom variations were analyzed in groups: 0–1 month, 1–2 months, 2–3 months, 3–4 months, and 4–6 months.



Results

413 out of 891 infants obtained complete information

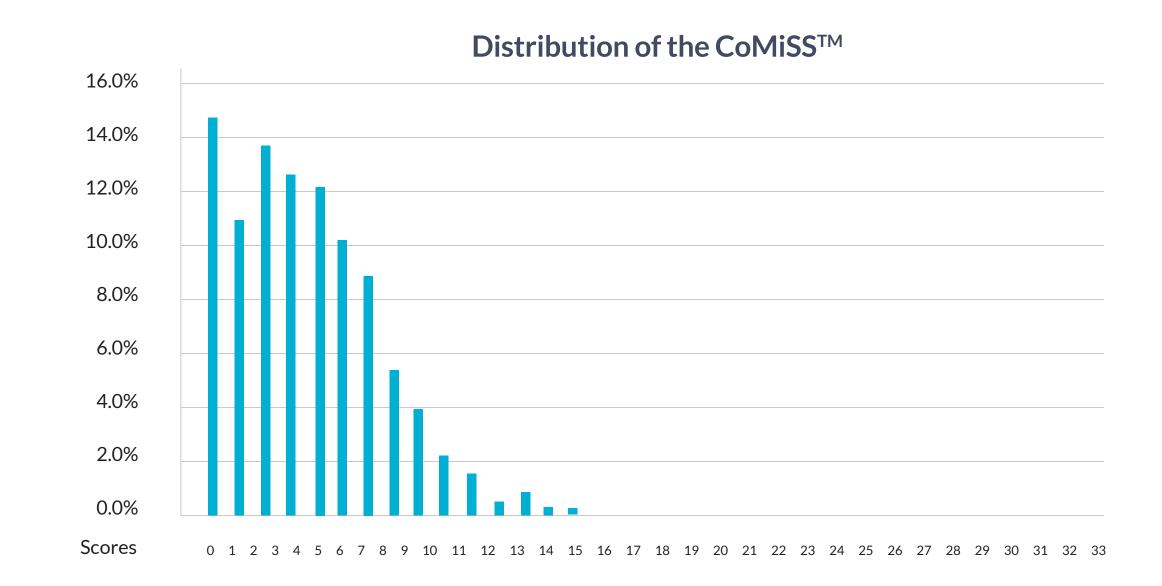
Age did influence the overall CoMiSSTM, in terms of each symptom

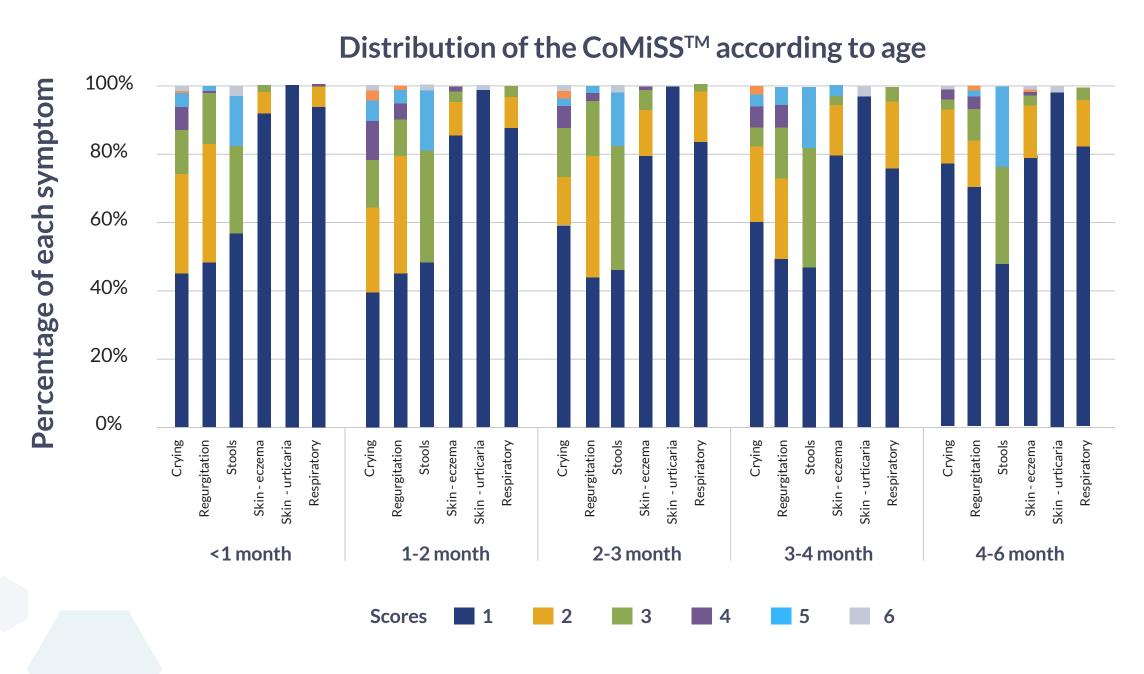
- Significant differences were observed in median crying (p<0.001), regurgitation (p=0.009), and eczema (p=0.04) scores across age categories, with crying time and episodes of regurgitation per day decreasing in older infants, while eczema was most frequently found in the lowest age categories.
- The other components of the CoMiSS™ (respiratory symptoms and stool consistency) were not age-dependent.

The median and mean (SD) CoMiSSTM score were 3.0 and 3.7 (2.9), respectively.

Only 1.5% of healthy infants in the study had a CoMiSSTM \geq 12, previously the threshold for a 'positive' score. Meanwhile, 95% of the infants scored \leq 9, indicating that a CoMiSSTM of 10 might be a more appropriate overall cut-off for a positive results.

75% of healthy infants had a CoMiSS[™] ≤ 6, indicating that a CoMiSS[™] of 6 could be a useful lower cut-off for negative results.





This study found median CoMiSS™ score for healthy infants at 3.0, mean at 3.7, and P95 at 9. Age significantly influenced overall CoMiSS™



TESTING THE COW'S MILK-RELATED SYMPTOM SCORE (COMISS™) FOR THE RESPONSE TO A COW'S MILK-FREE DIET IN INFANTS: A PROSPECTIVE STUDY

Salvatore S et al. Nutrients. 2019;11(10):2402.



Study objectives

To evaluate the accuracy of the CoMiSS™ in identifying infants who can benefit from Cow's Milk-Free Diet (CMFD) when Cow's Milk Allergy (CMA) is suspected.



Subjects and methods

An open prospective study in 47 infants (cases) who began CMFD due to acute or gastrointestinal symptoms suspected for CMA.

CoMiSS™ scores were assessed at enrollment (T0), and after 2–4 weeks of CMFD (T1) and were compared to the score of healthy infants (controls, obtained at T0).

- CoMiSS™ was evaluated at inclusion and after 3 weeks ± 5 days.
- Responsive to CMFD' was defined as any infant whose CoMiSS™ score was higher than the
 average (median) of the case group at T0 but then fell below the average of the control group at T1.



Endpoints

Primary endpoints: Sensitivity and specificity of CoMiSS™ in identifying infants who respond to CMFD

Secondary endpoints: The best cut-off CoMiSS™ score to predict the response to CMFD



Results

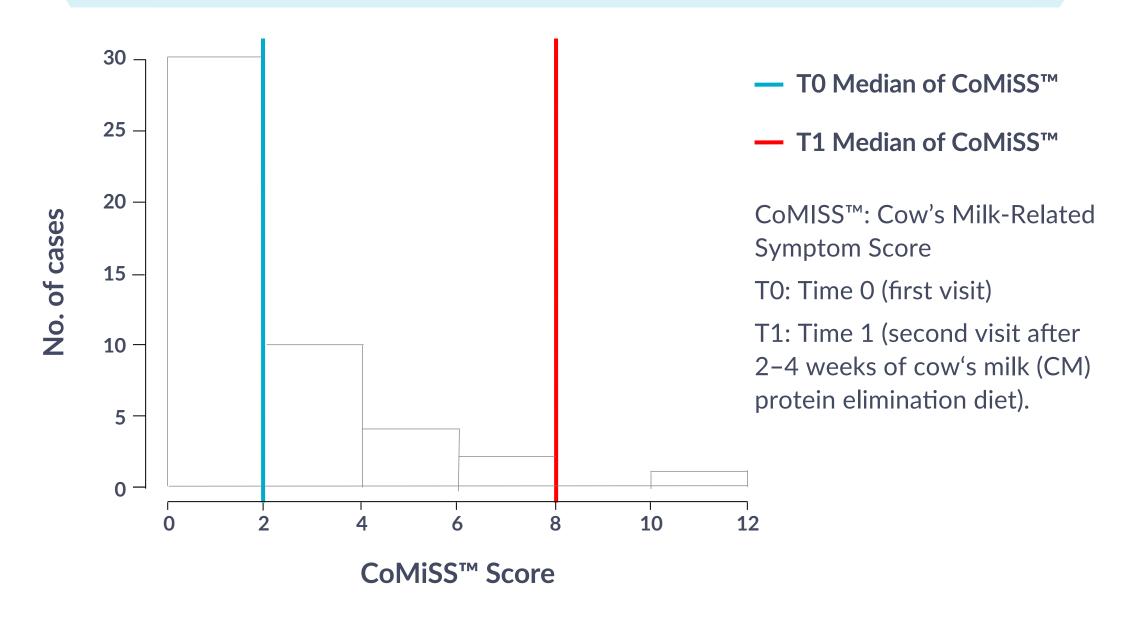
- At T0 (enrollment), the median score of CoMiSS™ was 8 (range 2–16) in cases and 3 (range 0–11) in controls.
- Median CoMiSS™ score decreased from 8 at T0 to 2 at T1 (the end of the CMFD)
- The median CoMiSS™ score was significantly higher in infants who benefited from the diet compared to those who did not show a response.

Out of 47 symptomatic infants:

- 39 (83%) had a reduction of symptoms on the CMFD
- 19 (40%) had a significant response to CMFD
- 6/19 (31.6%) had a positive reaction to CM after an oral milk challenge
- Only 9 (19%) had a CoMiSS™ score ≥12 at T0, and 8/9 (89%) had a negative (<12) score at T1.

The score of 9 was identified as the best cut-off for the test with 91% of the real positive infants.

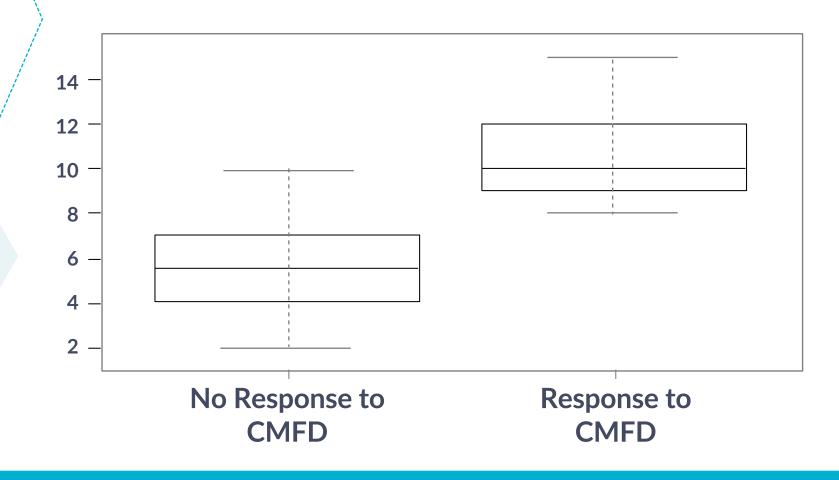
Decrease of the CoMiSS™ score in cases on cow's milk-free diet (CMFD) (T1)



CoMissTM

proves to be a valuable tool in identifying infants who would benefit from CMFD when CMA is suspected.

Box plot distribution of CoMiSS™ at baseline comparing infants who responded and did not respond to CMFD.





THE COW'S MILK-RELATED SYMPTOM SCORE (COMISS™): HEALTH CARE PROFESSIONAL AND PARENT AND DAY-TO-DAY VARIABILITY*

Vandenplas Y et al. Nutrients. 2020; 12(2):438.



Study objectives

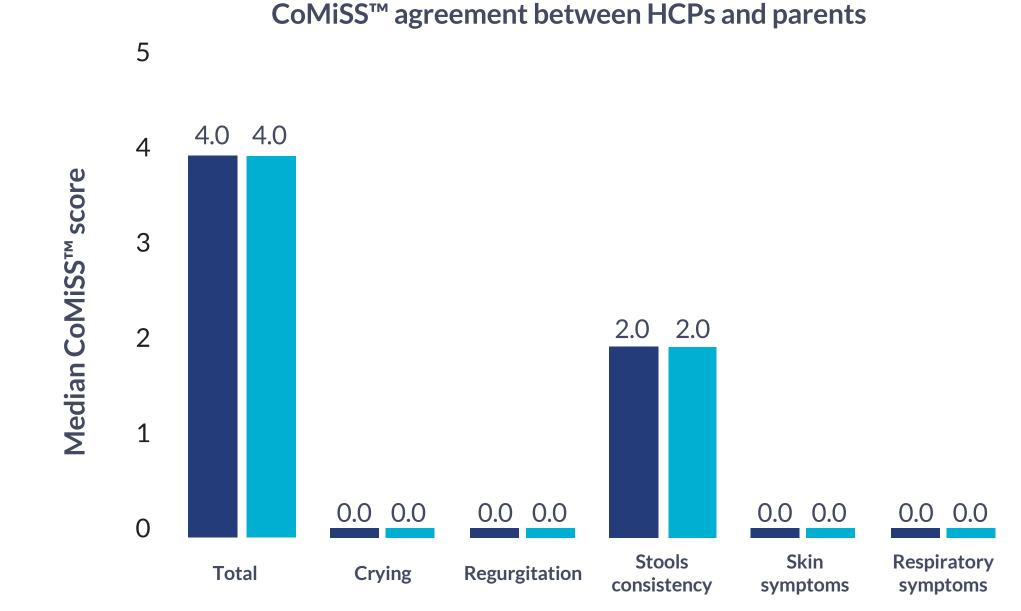
To assess the inter-rater reliability of the CoMiSS™ between parents and health care professionals (HCPs) and the day-to-day variability of the CoMiSS™ over four consecutive days.



Subjects and methods

A comparison of CoMiSS[™] between parents and HCPs was conducted in Spanish healthy infants aged 2–6 months old (n=148). Pediatricians scored the CoMiSS[™] based on the history and the physical exam, while parents, blinded to the pediatrician's score, filled in a second CoMiSS[™] after the routine visit.

The 4-days CoMiSS[™] variability was assessed in Belgian infants aged <6 months old (n=72), comparing the CoMiSS[™] obtained by HCPs (t1) and parents (on t2) and between the parental CoMiSS[™] recorded on three consecutive days (t2-t4).





Endpoints

CoMiSS[™] scored by parents and HCP.



Results

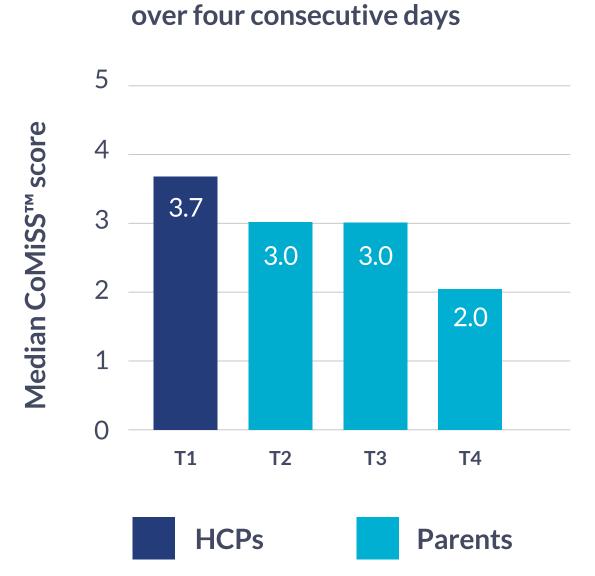
HCP versus Parents: No significant differences were found in CoMiSS™ symptoms or total scores

• The agreement between parents and HCPs was 75%, reaching 92.6% and 100% with tolerances of 0, 1, and 2 points.

4-days CoMiSS™ Variability: very low variability was observed when prospectively scoring the CoMiSS™ over three days

- The agreement between healthcare providers (HCPs) and parents was 25% on t1 vs. t2, increasing to 68.1% (with a 2-point tolerance) and 77.8% (with a 3-point tolerance)
- The agreement for the CoMiSS™ by a parent on t2–t4 was 30%, which increased to 80% and 88.6% when a tolerance of respectively 2 and 3 points were accepted.

The variability of the CoMiSS™ scored prospectively over three days was very low. Simultaneously, the similarity in scoring between parents and healthcare providers indicates that the CoMiSS™ can be reliably scored by parents without additional training



Day-to-day variability of the CoMiSS™

The agreement for CoMiSS™ between parents and pediatricians was excellent, indicating that parents can reliably record the CoMiSS™ at home or in the waiting room before a consultation, with no special training required.

* The CoMiSSTM Expert Consensus Panel recommends that CoMiSSTM is used by the HCP in conjunction with the Parent/caregiver, not the Parent/caregiver alone





HOW ARE INFANTS SUSPECTED TO HAVE COW'S MILK ALLERGY MANAGED? A REAL WORLD STUDY REPORT

Vandenplas Y et al. Nutrients. 2021 Aug 30;13(9):3027



Study objectives

To assess the diagnosis and management of infants with symptoms linked to CMA in real-world conditions and to explore how the Cow's Milk-related Symptom Score (CoMiSSTM) can aid in increasing awareness and diagnosing CMA in primary care practice.



Subjects and methods

A multicenter prospective observational single-cohort study in infants aged 0 to 18 months (n=268) with suspected mild to moderate symptoms of CMA.

- CoMiSSTM was evaluated at inclusion and after 3 weeks \pm 5 days.
- A satisfaction questionnaire about the use of the CoMiSS™ awareness tool was completed by each healthcare provider (HCPs) at the end of the study.

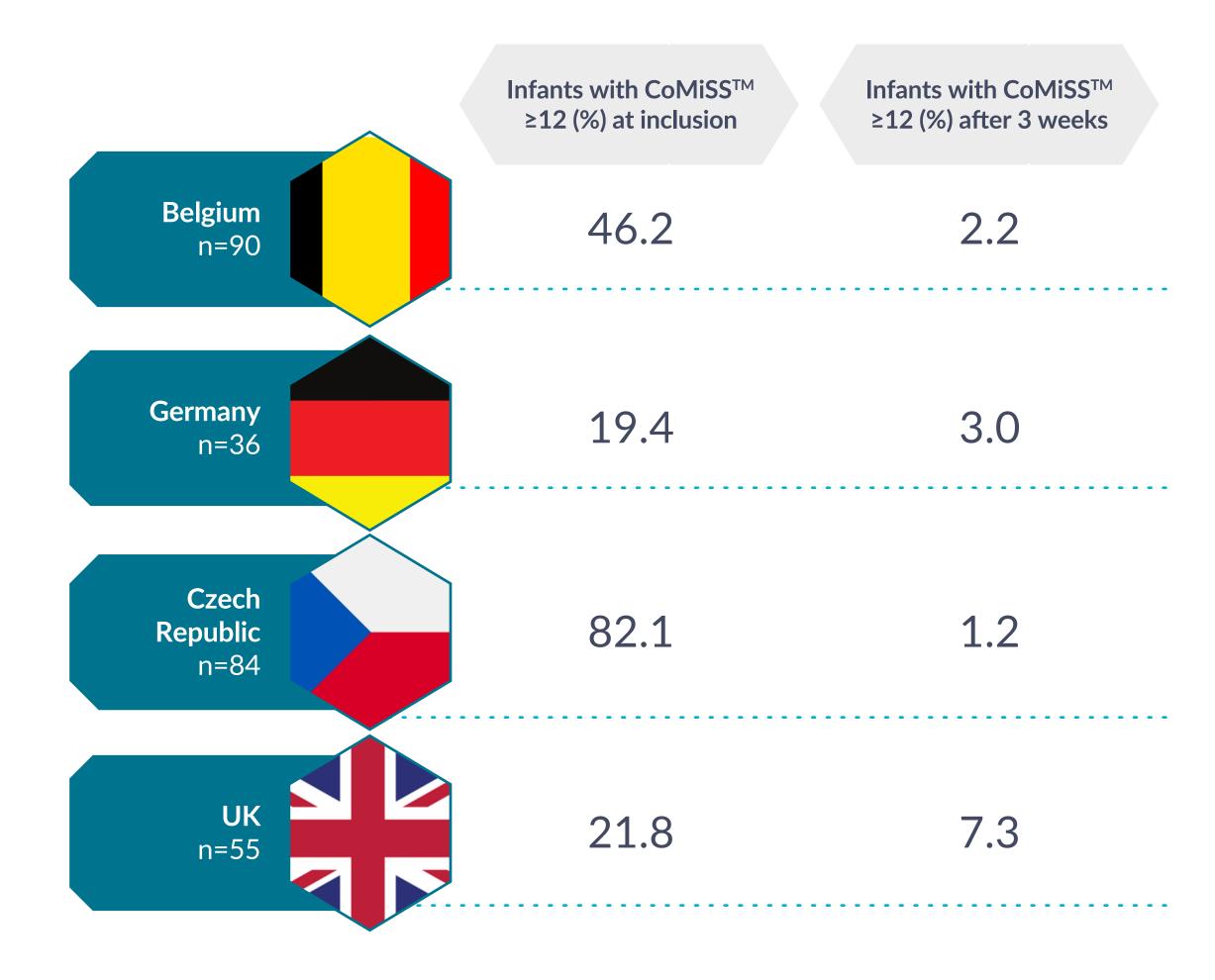


Results

From inclusion to after therapeutic dietary intervention, the reduction in mean and median CoMiSSTM was 6.9 (from 11.1 to 4.2) and 7 (from 11.0 to 4.0), respectively. Moreover, the number of infants who had a CoMiSSTM \geq 12 and \geq 9 fell from 48.9% to 1.5% (4/268 infants) and 72.3% to 8.6% (23/268 infants), respectively.

An open oral food challenge to confirm CMA was conducted in 17 infants, with 4 (24%) testing positive. Initially, blood tests, including IgE tests, were significantly more requested for infants with a CoMiSSTM \geq 12, while skin prick tests were less commonly performed in this group.

CoMiSS™ ≥12: "at risk" for cow's milk allergy





THE COW'S MILK RELATED SYMPTOM SCORE: THE 2022 UPDATE

Vandenplas Y et al. Nutrients. 2022;14(13):2682.



Study objectives

To propose an updated Cow's Milk Related Symptom Score CoMiSS™ based on extensive research using the tool since its first development in 2014 and publication in 2015.



Subjects and methods

10 international experts, collectively reviewed and discussed published data on CoMiSS™, since its first publication in 2015. Potential modifications were debated, including the removal or addition of symptoms. Each member voted for the proposed updates by marking "agree," "abstain," or "disagree" beside each statement.



Endpoints

Agreed statements regarding the updates to CoMiSSTM



Results

All statements achieved more than 80% agreement, with updates including:

- (100%) Overall cut-off score reduced from ≥12 to ≥10
 because a score of ≥12 was deemed to have low sensitivity.
 High sensitivity was considered crucial to ensure the
 detection of more 'true' positives.
- A lower cut-off of <6 was included, because a score of <6
 was considered predictive of the absence of CMA.
- (90%) Bristol Stool Scale (BSS) was replaced by Brussels Infant and Toddlers Stool Scale (BITSS), which better reflects the stool consistency of non-toilet trained infants.
- (80%) Angioedema added to acute urticaria because angioedema and urticaria frequently co-exist, and result from similar mechanisms associated with CMA.

2022 CoMiSSTM Update

Updated Components of CoMiSS™

Gastrointestinal symptoms

Bristol Stool Scale replaced by Brussels Infants and Toddlers Stool Scale

Dermatological symptoms

Angioedema added to acute urticaria

- >1 week should be added to each symptom category to avoid scoring acute causes which are NOT often related to CMA.
- Additional information was also added to be clear for whom the tool is not intended and when immediate referral is required.

CoMissTM

was updated in 2022 and remains a useful awareness tool for the assessment of cow's milk-related symptoms in infants up to 12 months of age.

Interpretation of final score

<6

Suggests other causes should be investigated

≥10

Suggests higher likelihood of CMA

CMA: Cow's milk allergy



THE COW'S MILK-RELATED SYMPTOM SCORE (COMISSTM): A USEFUL AWARENESS TOOL*

Bajerova K et al. Nutrients 2022; 14(10), 2059.



Study objectives

To summarize available research and evidence for CoMiSS™, particularly its contribution as an awareness tool in the management of infants suspected to have CMA.



Subjects and methods

28 published papers in databases like NCBI/Pubmed, NCBI/PMC, EBSCO/Academic Search Ultimate, and Ovid/Embase, were identified up to 19 February 2022:

25 original studies involving over 3000 infants 1 pooled analysis of 3 studies, and 2 reviews on CoMiSS™



Results

Infants showing symptoms possibly related to CMA had a higher median CoMiSS™ (6 to 13; 16 studies) than healthy infants (3 to 4; 5 studies).

A CoMiSS™ ≥12 predicted a positive response to a CM-free diet in infants with CMA

A significant decrease in CoMiSS™ scores is noted in those with a score
 ≥12 when following a CM elimination diet, regardless of the clinical symptoms and IgE levels.

A CoMiSS™ <6 was predictive for the absence of CMA. The reliability of repeated assessments was very high and consistent, with an intra-class correlation of 0.93 (meaning there was very little change between their ratings) (p<0.001).

HCPs who used CoMiSS™ in their daily practice found it a helpful and fast-to-use tool, which can be reliably used without the need for special training.

CoMiSS™ helps increase awareness of the most common symptoms associated with CMA supporting earlier diagnosis

CoMiSS™ cannot be considered as a stand-alone diagnostic tool for CMA

KEY FEATURES

- The only tool that raises awareness of CMA symptoms
- Simple, fast and easy to use

POTENTIAL BENEFITS

Symptom monitoring before and during an CM elimination diet

A high baseline CoMiSS™
 associated with a significant
 reduction during a CM
 elimination diet

CoMissTM

is a simple, fast and easy to use awareness tool for CMA and monitoring symptom improvement.

CoMiSS™ score

<6

Predictive for the absence of CMA

≥12

Predictive for a positive response to a CM-elimination diet

CMA: cow's milk allergy, CM: cow's milk





ASSESSMENT OF THE COW'S MILK-RELATED SYMPTOM SCORE (COMISS™) AS A DIAGNOSTIC TOOL FOR COW'S MILK PROTEIN ALLERGY: A PROSPECTIVE, MULTICENTRE STUDY IN CHINA (MOSAIC STUDY)

Vandenplas Y et al. BMJ Open. 2022;12:e056641.



Study objectives

To assess if CoMiSS™, initially created as an awareness tool, can also serve as an independent diagnostic tool for infants with CMPA.



Subjects and methods

The prospective, single-blind, multicenter study was conducted in non-breastfed infants aged ≤6 months with suspected CMPA. Infants underwent a 2-week cow's milk protein (CMP) elimination diet with an amino acid based formula AAF (Alfamino®), followed by a standardized hospital-based oral food challenge (OFC) and a 2-week home-based challenge.

• CoMiSSTM was evaluated at inclusion and at the end of the elimination trial.



Endpoints

Area under the curve (AUC)

• AUC ≥0.75 was considered sufficient to validate CoMiSS[™] as a diagnostic tool, aiming for a sensitivity of 80%-90% and a specificity of 60%-70%



Results

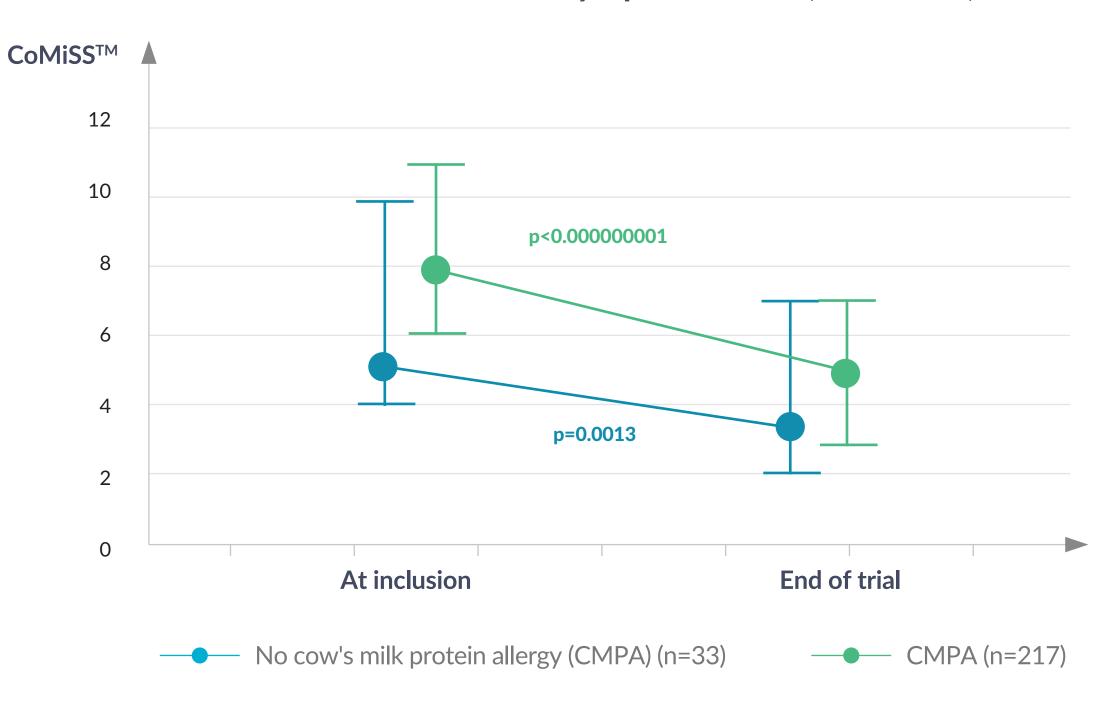
Out of 300 infants, 250 completed both OFC and CMP challenges, 217 were confirmed to have CMPA.

- AUC was 0.67 (I.e. <0.75), therefore could not be considered diagnostic
- An inclusion CoMiSS[™] of ≥12 showed low sensitivity (20.3%) but high specificity (87.9%) and a high positive predictive value (91.7%) for identifying CMPA.

Among 217 infants with CMPA, CoMiSS™

- At inclusion was higher (8) compared to CMPA-negative infants (5)
- Significantly decreased from inclusion to the end of the CMP elimination diet (from 8 to 5), a higher reduction than infants without CMPA (from 5 to 3.5). This suggests a potential role for CoMiSSTM in monitoring the response to a diagnostic elimination diet.

Total Cow's Milk-related Symptom Score (CoMiSS™)



CoMiSS™

was not concluded to be a diagnostic tool for CMPA, but remains a clinically useful awareness tool to help identify infants with cow's milk-related symptoms.



COW'S MILK-RELATED SYMPTOM SCORE (COMISSTM): FROM BRISTOL TO BRUSSELS STOOL SCALE

Bajerova et al. Journal of Pediatric Gastroenterology and Nutrition. 2023 November 77(5):p 618-622



Study objectives

To assess if the Brussels Infants and Toddlers Stool Scale (BITSS) can be used in place of the Bristol Stool Form Scale (BSFS) in non-toilet-trained infants without affecting the reliability of CoMiSS™ results related to cow's milk allergy (CMA) awareness.





Subjects and methods

A prospective observational multicenter study, including subjects aged <13 months (n=294), who were assessed by CoMiSS™ using the 7 images from the BSFS (CoMiSS-BSFS) compared to the 4 images of stools from BITSS (CoMiSS-BITSS).

Brussels Infants & Todders Stool Scale (BITSS)





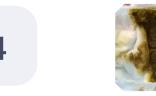






Formed

stools









Watery

stools



Significant difference Score ≤5: p<0.001

Compared CoMiss-Bsfs

vs. CoMiSS-BITSS

Non significant difference

Score ≥6: p=0.81 Score ≥10: p=0.84 Score ≥12: p=0.48

Using BITSS instead of BSFS in CoMiSS does not modify CoMiSS™ for values ≥6 and thus does not change the cutoff for infants in whom cow's milk-related symptoms cannot be excluded.

> CMA: Cow milk allergy, CoMiSS™: Cow's Milk-Related Symptom Score, BITSS: Brussels Infants and Toddlers Stool Scale, BSFS: Bristol Stool Form Scale



Results

With the original cutoff of ≥12, switching from BSFS to BITSS resulted in:

- only 2/844 infants (0.24%) moving from a score of below to above the cutoff
- only 1/844 infants (0.12%) moved from a score above to below the cutoff

With the revised cutoff of ≥ 10 :

- 3/844 infants (0.36%) shifted from below to above the cutoff
- no infants moved from a score above to below the cutoff

There were no significant differences in the groups with CoMiSS-BSFS scores of ≥ 6 (p=0.81), \geq 10 (p=0.84), \geq 12 (p=0.48) compared to CoMiSS-BITSS.

The significant difference was confined to the group with a CoMiSS-BSFS score of ≤5 (p<0.001)

Switching from CoMiss-Bsfs to CoMiss-Bitss preserves the established CMA awareness cutoff, with no impact on its clinical application





COW'S MILK-RELATED SYMPTOM SCORE (COMISS™) VALUES IN PRESUMED HEALTHY EUROPEAN INFANTS AGED 6-12 MONTHS: A CROSS-SECTIONAL STUDY

Jankiewicz, et al. Eur J Pediatr 183, 707-713 (2024).



Study objectives

The study aimed to assess CoMiSS™ values in healthy infants aged 6 to 12 months, facilitating better interpretation of these values for symptomatic patients within the common age range for diagnosing Cow's Milk Allergy (CMA).



Subjects and methods

Conducted internationally from September 2022 to April 2023, this multicenter cross-sectional study investigates healthy children aged 6 to 12 months attending clinics for routine follow-up visits or vaccinations, with comprehensive data collection encompassing gestational age, gender, age, type of feed (breast milk or infant formula), and details on complementary feeding.



Endpoints

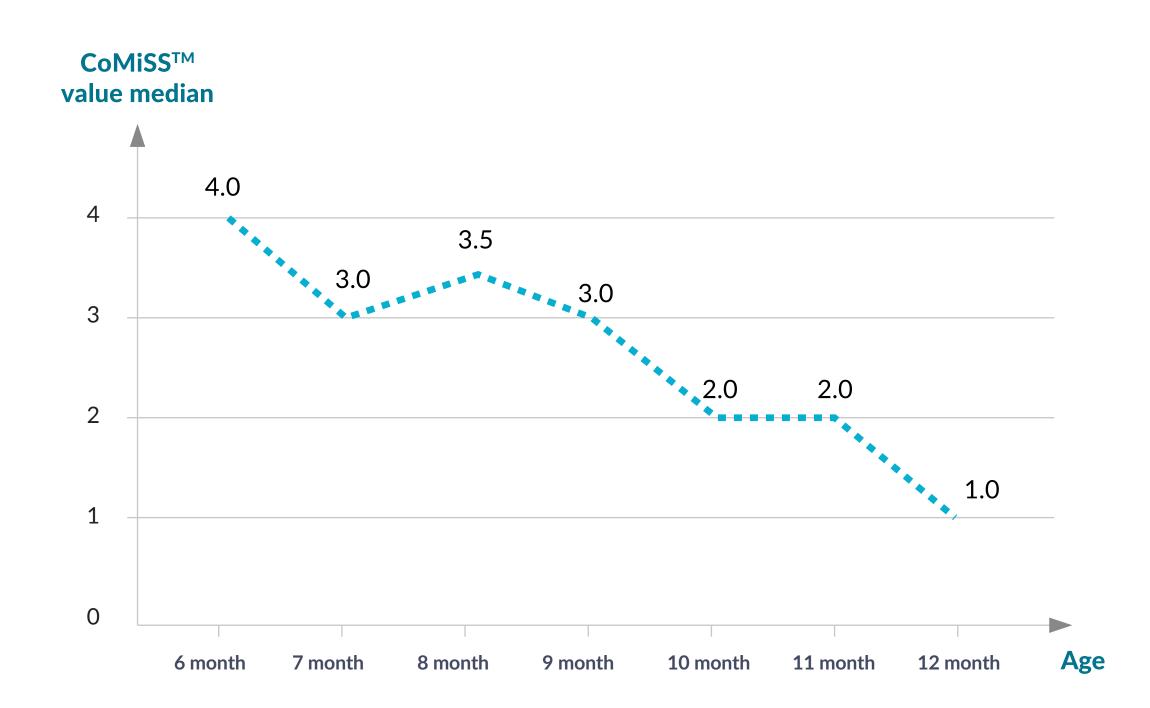
CoMiSS™ values in European infants aged 6 to 12 months.



Results

The overall median CoMiSSTM value was 3, with 1.3% of children having CoMiSSTM \geq 10. No differences in CoMiSSTM values were observed by gender or feeding type (including crying, skin, and respiratory symptoms). However, the total CoMiSSTM score varied by age, being highest at 6 months and lowest at 12 months, as seen in regurgitation and stool scores.

- 30% of infants at 6 months old exhibit a stool score of 4 or above
- 2.8% (17 infants) had regurgitation scores >3, primarily at 6 months (58%). None had total volume regurgitations, with only 0.2% (one infant) regurgitating half the volume in at least half of their meals.
- No infant exhibited severe respiratory symptoms.
- Only 1 infant (0.2%) reported experiencing urticaria.



The study expands
CoMiSS™ value data in healthy
European infants aged 6 to 12
months, emphasizing the influence of
age on CoMiSS™ values. Further
research is required to evaluate
CoMiSS™ as a tool for assessing
cow's milk-related symptoms in
infants beyond 6 months.





REFERENCE

- 1. Vandenplas Y et al. Nutrients. 2020; 12(2):438.
- 2. Vandenplas Y et al. PLoS One. 2018 Jul 18;13(7):e0200603.
- 3. Bajerova K et al. Nutrients 2022; 14(10), 2059.
- 4. Vandenplas Y et al. BMJ Open. 2022;12:e056641.
- 5. Yvan Vandenplas et al. Acta Pædiatrica. 2015;104(4):334-339.
- 6. Vandenplas Y et al. Nutrients. 2021 Aug 30;13(9):3027.
- **7.** Salvatore S et al. Nutrients. 2019;11(10):2402.
- 8. Bajerova et al. Journal of Pediatric Gastroenterology and Nutrition. 2023 November 77(5):p 618-622.
- 9. Jankiewicz M, et al. Eur J Pediatr 183, 707–713 (2024).
- 10. Vandenplas Y et al. Nutrients. 2022;14(13):2682.

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User Guide



2022 Tool

In 2022, updates were made to CoMiSSTM. The updated CoMiSSTM and User Guide can be downloaded using the QR code.



