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REVIEW

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Cultural and Clinical Dimensions of Milk Ladder Therapy: A Narrative Review from the Asian Context

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ABSTRACT

Milk ladder (ML) therapy has emerged as a structured, evidence-based approach for the reintroduction of cow's milk protein in children with allergy, offering a gradual progression from extensively heated products to less processed forms. While ML demonstrates high efficacy in non-IgE-mediated CMPA due to its lower risk profile, its application in IgE-mediated cases requires stringent patient selection and clinical oversight. Globally, ML protocols have been adapted to reflect local dietary practices, yet implementation across Asia remains inconsistent. The absence of standardized regional guidelines, limited clinical validation, and cultural misalignment with Western-based food stages hinder widespread adoption. In Southeast Asia, ML is not formally integrated into national allergy frameworks, resulting in informal adaptations that vary in safety and reproducibility. Recent studies from Japan and Korea suggest that ML and oral immunotherapy (OIT) yield comparable outcomes in tolerance induction, though ML offers greater accessibility and cultural flexibility. To ensure safe and effective implementation, ML protocols must incorporate allergy phenotype stratification, caregiver education, and emergency preparedness. Developing culturally appropriate food stages using locally available ingredients and traditional cooking methods is essential for improving adherence and clinical outcomes. Multidisciplinary collaboration among clinicians, dietitians, and food scientists is critical to establish validated, context-sensitive ML frameworks. With appropriate adaptation, ML therapy holds promise as an inclusive and sustainable strategy for CMPA management across diverse Asian populations.

Keywords: Cow's milk allergy, milk ladder, Asia, cultural adaptation, clinical safety

INTRODUCTION

Cow's milk protein allergy (CMPA) affects up to 3% of children worldwide, with varying prevalence rates across different regions. In Asia, epidemiological data is sparse, but emerging studies suggest a rising trend, particularly in urbanized areas. Traditionally, CMPA management has relied on strict avoidance of cow's milk protein until spontaneous tolerance develops (1). While effective in preventing allergic reactions, prolonged avoidance may delay the acquisition of tolerance and negatively impact dietary diversity (2).

The milk ladder (ML) approach offers an alternative: a structured, stepwise reintroduction of milk protein, beginning with extensively baked products, in which heating denatures allergenic proteins, and progressing to less processed forms. This method not only supports earlier tolerance but also empowers families through home-based management under professional guidance. Although well-established in the UK and Ireland, its adoption in Asia is inconsistent, with adaptations often occurring informally in clinical practice (3).

GLOBAL EVIDENCE ON THE MILK LADDER

The ML is a stepwise approach for the reintroduction of CMPA in children with allergies, beginning with extensively heated products such as baked goods and progressing toward fresher, less denatured forms. This strategy

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aims to safely accelerate the development of immunological tolerance while mitigating the negative impact of prolonged elimination on nutritional diversity and quality of life (3). Beyond its clinical benefits, the approach empowers families through home-based monitoring under healthcare supervision, which has been shown to enhance engagement and therapeutic success (4).

The highest efficacy is observed in non-IgE-mediated CMPA cases, which typically present with delayed gastrointestinal symptoms and carry a lower risk of severe reactions. In IgE-mediated cases, the protocol remains applicable with strict patient selection and intensive clinical oversight, making allergy phenotype identification a critical factor for safe implementation (5).

Globally, ML protocols have been adapted to local contexts. In the United Kingdom and Ireland, protocols consist of 4 to 12 stages, supported by specific food guides and structured educational resources. Meanwhile, countries such as Spain and Italy have modified the stages to align with traditional dietary patterns (6). These differences underscore the importance of flexible, evidence-based protocols that can be tailored to cultural diets and healthcare systems. As summarized in Table I, global variations in ML implementation reflect differences in the number of stages, types of foods used, and levels of protocol validation, underscoring the need for both cultural and clinical adaptation (7-12).

In practice, structured home-based approaches, when supported by comprehensive caregiver education, including training in food label interpretation, symptom recognition, and progress tracking, have proven effective in facilitating tolerance development and enhancing caregiver confidence in allergy management (4).

Table I: Overview of milk ladder implementation studies in several countries.

Countries	Population and target	Milk Ladder	Success	Duration	References
UK	86 children <3 years with IgE-mediated CMPA (mild to moderate symptoms)	Four stages based on home-prepared and commercial food products	- Most children attained complete tolerance. - 8 children remained intolerant to nearly all dairy products. - 7 children withdrew from the program.	Over a period of 12 to 18 months	Ball & Luyt (7)
Ireland	82 children with IgE-mediated CMPA (13 children in primary care); with an average age of 8.5 months (primary care) and 11.14 months (tertiary care)	iMAP Guideline (12-step ladder)	- 85% success (primary care) - 83% success (tertiary care)	- Average of 12.7 months (primary care) - Average of 15.5 months (tertiary care)	Cronin et al. (8)
Ireland	171 children (majority of <3 years)	Adaptation of the MAP guideline – 12-step framework	86.6% success; ≥150 mL milk tolerated symptom-free	≤3 years	Ah Heng et al. (9)
Ireland	171 children <3 years with IgE-mediated CMPA (36 children with anaphylaxis)	MAP guideline 12 steps	- 77.8–85.2% success (anaphylaxis history) - 88.9–92.9% success (without anaphylaxis history)	- ± 20.7 months (anaphylaxis history) - ± 17.8 months (without anaphylaxis history)	Gallager et al. (10)
Spain	Children with IgE-mediated CMPA	Adapted Version of the Milk Ladder (AVML) – Four Progressive Stages.	Currently undergoing the research process.	± 12 months	Cerecedo et al. (11)
Japan	38 children with an average age of 1.21 years	Modified milk ladder protocol (baked milk to less processed forms)	- 47% achieved tolerance to ≥100 mL liquid milk without symptoms - 76% tolerated low milk processed products	2 years after intervention	Matsumoto et al. (12)

CURRENT STATUS OF MILK LADDER IN ASIA

In Asia, the absence of a formal ML protocol reflects a systemic gap in the management of CMPA. Without national guidelines or regional consensus, clinical practice relies heavily on informal adaptations of Western protocols such as MAP/iMAP, which often fail to align with local cultural contexts, dietary patterns, and resource availability. This inconsistency affects the quality of care, increases the risk of errors during reintroduction, and raises concerns about patient safety, particularly in areas with limited access to allergy specialists or monitoring facilities (13,14).

This phenomenon is particularly evident in Southeast Asia, where ML is not yet incorporated into national guidelines, as observed in Indonesia, Malaysia, and the Philippines. As a result, milk reintroduction is driven by individual initiatives, primarily in private clinics that adopt Western protocols without contextual adaptation. Disparities in access between urban centers and rural areas are further exacerbated by insufficient training of primary healthcare providers, limited caregiver education, and the lack of standardized recipes using locally available ingredients. Technical barriers, such as inconsistent food labeling and parental anxiety over allergic reactions at home also hinder the desensitization process (14,15).

To address these challenges, a shift toward culturally adaptive ML protocols is urgently needed. Developing an Asian version should incorporate commonly used ingredients such as rice flour, coconut milk, and fermented products, along with traditional cooking methods that influence milk protein denaturation. The design of ML stages must also reflect local eating habits and be supported by rigorous clinical validation to gain legitimacy within national healthcare systems. Cross-disciplinary collaboration among clinicians, researchers, and policymakers is essential to bridge local innovation with global standards (14).

Figure 1 presents a summary of ML adaptations across various Asian countries, highlighting examples of local foods, processing techniques, and levels of clinical validation. This visualization reinforces the need for safe, standardized, and contextually relevant ML protocols tailored to the diverse populations of Asia (12,16-18).

CULTURAL and DIETARY ADAPTATIONS IN MILK LADDER IMPLEMENTATION

The diverse culinary landscape of Asia presents both challenges and opportunities in localizing the ML protocol. In line with this diversity, the wide range of traditional foods, cooking techniques, and religious dietary regulations necessitates adaptations that extend beyond simple ingredient substitution (3). In Indonesia, for example, the use of steamed sponge cake (*bolu kukus*) or layered cake (*kue lapis*) as initial ML steps requires careful calibration of processing time and temperature, as steaming generates lower thermal intensity than baking, potentially resulting in incomplete denaturation of milk proteins (19).

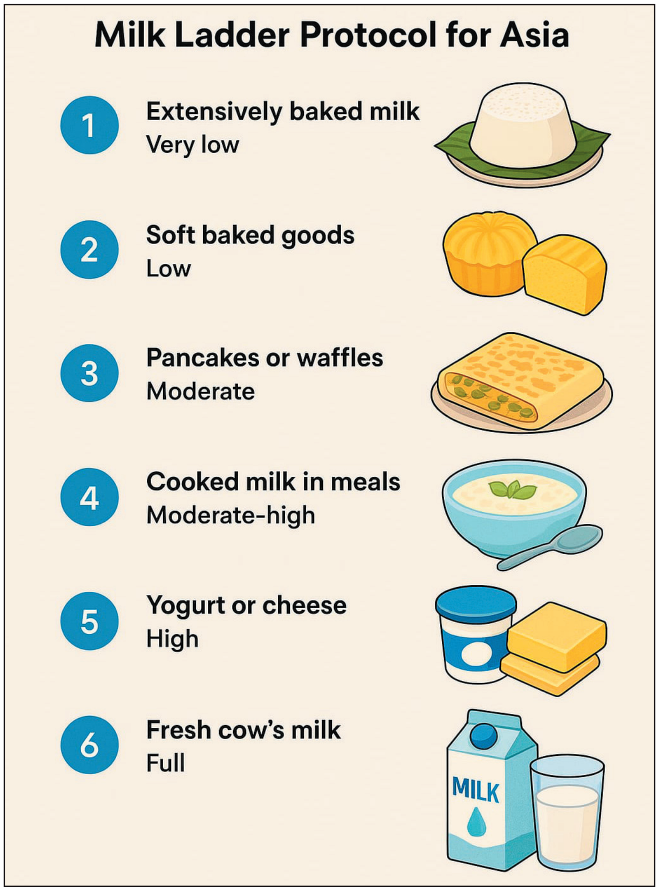

Figure 1: Culturally Adapted Milk Ladder Protocol for Asia. A six-step milk reintroduction framework tailored for Asian dietary contexts, progressing from extensively baked milk products to fresh cow's milk. Each stage represents increasing levels of milk protein exposure: (1) extensively baked milk in rice-based items (very low), (2) soft baked goods such as sponge cake or muffin (low), (3) pancakes or crepes (moderate), (4) cooked milk incorporated into meals like porridge or soup (moderate-high), (5) fermented dairy products including yogurt and cheese (high), and (6) fresh cow's milk (full exposure). This ladder supports gradual desensitization in children with cow's milk allergy, emphasizing culturally relevant food forms to improve adherence and safety in Asian populations.

Expanding on these adaptation examples, India illustrates an even clearer need for culturally grounded modifications through the development of the Indian milk ladder, which not only incorporates local food preferences but also empirically validates processed protein content (Figure 2). Furthermore, the use of *kheer*, *ragi dosa*, and *halma* has been shown to produce significant protein denaturation, as demonstrated by laboratory analyses of processed protein content at each ladder step. These findings are reinforced by Ramakrisna *et al.*, who emphasize that empirical validation of denatured protein levels is essential to ensure safety and consistency when implementing the ladder across diverse cultural contexts. Collectively, this approach underscores that ML adaptation cannot rely solely on assumptions about heating effects; instead, it must incorporate objective measurements of residual protein content following food preparation (18).

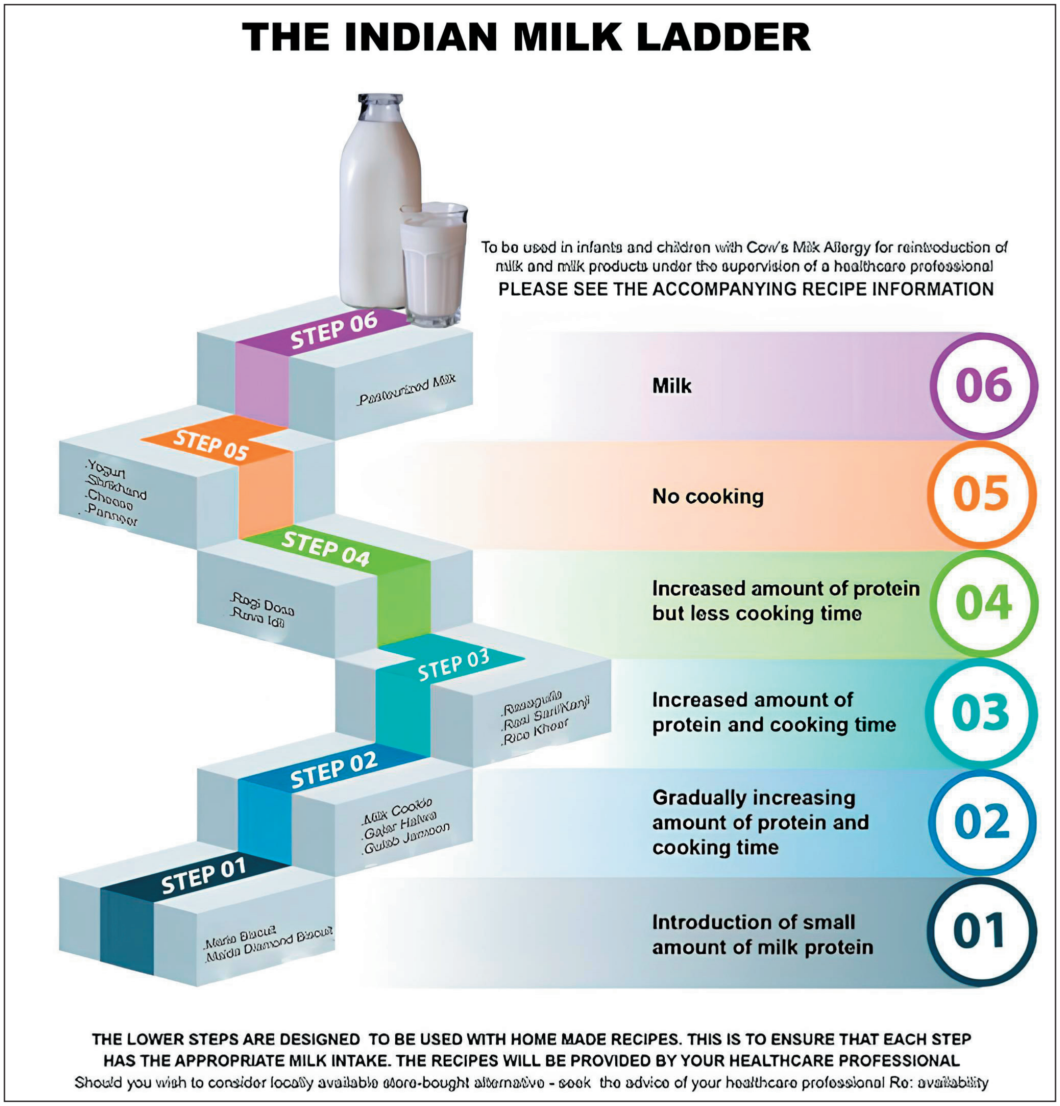

Figure 2: The Indian milk ladder. One example of a milk ladder developed in the Asia region is the Indian milk ladder. This diagram illustrates six steps of reintroducing milk and milk products in children with CMPA under the supervision of healthcare professionals. Each step represents a gradual increase in milk protein content and variation in heating intensity, beginning with the safest foods (such as baked biscuits) and progressing toward unheated forms of milk. In steps 1-4, foods are processed at high temperatures with varying heating durations to reduce allergenicity, whereas steps 5-6 include unheated products such as yogurt, paneer, and pasteurized milk. Overall, this protocol is designed to ensure safety, gradual tolerance development, and ease of adaptation to local culinary practices in India (18).

Consistent with these cross-country adaptation patterns, other culturally appropriate examples include *ka'ak* and *ma'amoul* in the Middle East, which require standardized preparation methods and allergen quantification (17). In Korea, *gyeran-ppang* and *hotteok* offer potential ML adaptations, although variants containing nuts or seeds necessitate additional allergen screening (20). Beyond traditional food, the growing popularity of standardized commercial milk bread also presents opportunity for more consistent ML implementation. Meanwhile, in Japan, *castella* and *dorayaki* are culturally familiar and consistently processed, yet the population's low dairy intake and reliance on soy-based alternatives require individualized assessment (12,21).

Integrating these findings, sensory familiarity with local foods enhances patient acceptance and adherence to ML. However, recipe variability, household preparation methods, and limited access to standardized ingredients pose challenges to reproducibility and cross-study validation. As summarized in Table II, India and Malaysia have established validated frameworks, whereas Indonesia, Korea, and the Middle East remain in exploratory or adaptive phases (12,16-18). The implication of these differing exploratory approaches underscore the importance of collaboration among allergists, nutritionists, and food scientists to develop ML recipes that are both culturally appropriate and clinically sound, with clearly defined protein content and denaturation profiles. Moreover, such modifications not only improve clinical safety but also support the equitable and context-sensitive implementation of allergy protocols across Asia's heterogeneous populations (5,6,22).

SAFETY CONSIDERATIONS IN MILK LADDER IMPLEMENTATION

The safety of implementing the ML protocol relies on accurate risk stratification, adequate clinical supervision, and preparedness for allergic reactions. Accordingly, the protocol must be tailored to the patient's allergy phenotype, particularly in distinguishing between IgE-mediated and non-IgE-mediated CMPA. Non-IgE-mediated CMPA typically presents with delayed gastrointestinal symptoms and carries a lower risk profile, allowing for gradual ML initiation at home with structured education and monitoring. In contrast, IgE-mediated CMPA poses a higher risk of acute hypersensitivity reactions, including anaphylaxis, and therefore requires specialist evaluation and reintroduction in a controlled clinical setting (5,23,24).

Based on these principles of risk stratification, the choice of initiation setting, home or healthcare facility, must be guided by a comprehensive risk assessment. Patients with a history of anaphylaxis, uncontrolled asthma, or severe atopic dermatitis should begin ML under direct medical supervision. In such cases, facilities must be equipped with emergency management protocols, including access to epinephrine autoinjectors and caregiver training in their use. In addition, clinical guidelines should define criteria for step regression, temporary discontinuation, and escalation procedures in the event of adverse reactions (25-27).

Beyond these clinical considerations, psychosocial factors also play a critical role in the success of ML. Consistent with this, Chua et al. emphasize that the success of ML is strongly influenced by careful patient selection and close

Table II: Comparative overview of milk ladder protocols across Asia and the Middle East.

Region	Number of Steps	Example food in Initial Steps	Protocol Status	References
Indian	6 steps	Marie biscuit, Maida diamond biscuit	Standardized and validated	Ramakrishna et al. (18)
Japan	Not explicitly defined	Baked milk, cookies, pizza	Clinically applied, not standardized	Matsumoto et al. (12)
Malaysia	4 steps (implicit)	Muffin, pancake, pizza, yoghurt	Recommended in national CMPA guidelines	CMPA Guidelines Malaysia 2024 (16)
Indonesia	Not yet standardized	Steamed sponge cake (bolu kukus), layered cake (kue lapis) with milk	Adaptation in progress	No formal publication
South Korea	Not yet standardized	Egg bread (gyeran-ppang), sweet pancake (hotteok), milk bread	Potential for commercial adaptation	No formal publication
China	Not yet standardized	Milk-filled mantou, egg tart with milk	Hospital-based adaptation	No formal publication
Middle East	Not yet standardized	Ka'ak, ma'amoul, baked milk bread	Clinically applied, not standardized	El-Hodhod et al. (17)

monitoring, which not only reduces the risk of reactions but also provides families with a sense of security. Furthermore, a clearly structured ladder (beginning with safest, most extensively processed foods and progressing to less processed forms) helps parents understand the therapeutic pathway and increases their readiness to continue the steps at home (23). These findings are reinforced by d'Art et al., who report that a safe initial experience through physician-supervised low-dose milk exposure probably (give) parents the confidence to proceed, thereby accelerating the child's progression through the ladder. Similarly, the significant reduction in maternal anxiety observed during therapy demonstrates that perceived safety is directly linked to adherence (28).

Evidence regarding the role of safety in building parental confidence is also consistent in high-risk populations. Gallagher et al., studying high-risk children (including those with a history of anaphylaxis) found that a safe and standardized ladder protocol still achieved high success rates, with no cases of ladder-induced anaphylaxis. These findings suggest that the absence of severe reactions during protocol implementation can strengthen parental trust and support consistent progression through the ladder (10). In line with this, Wiszniewska et al. emphasize that although parental anxiety and food aversion are more pronounced in high-risk IgE-mediated CMPA, a clear and safe leader protocol can mitigate these barriers and enhance family engagement (22,29). Overall, the safety of ML is determined not only by clinical factors and risk stratification but also by the protocol's ability to build trust, reduce anxiety, and improve parental adherence, ultimately contributing to successful reintroduction and accelerated acquisition of tolerance (10,22,23,28,29).

BARRIERS TO MILK LADDER IMPLEMENTATION IN ASIA

There is a pressing need for multicenter trials in Asia to evaluate the safety, efficacy, and cultural acceptability of adapted ML protocols. Standardized, validated recipes using locally available ingredients should be developed and tested. Integration of the ML into broader oral immunotherapy strategies could further enhance tolerance induction. Cost-effectiveness analyses are also warranted, particularly in low- and middle-income settings where healthcare access is limited (3,18,28).

Lack of Regional Guidelines

The absence of standardized ML protocols across Southeast Asia, East Asia, and South Asia represents a foundational barrier to safe and consistent implementation. Most clinicians in the region rely on adaptations of Western frameworks such as the MAP or iMAP guidelines, which were developed in contexts with distinct dietary norms, healthcare infrastructure, and allergy prevalence. These imported models often fail to account for local cooking techniques, food matrices, and cultural preferences, resulting in protocols that may be clinically inappropriate or difficult to operationalize. In IgE-mediated cases, where precision in allergen exposure is crucial, the absence of region-specific guidance can result in inconsistent application and an increased risk of adverse reactions. Establishing locally validated protocols through consensus panels and multicenter collaboration is essential to ensure both safety and cultural relevance (3,26).

Limited Clinical Trials in Asian Populations

Despite the growing interest in ML therapy, clinical evidence from Asian populations remains scarce. Most published studies originate from Europe, North America, or Turkey, leaving a significant gap in understanding how ML protocols perform in genetically, environmentally, and culturally distinct Asian cohorts. The lack of prospective and retrospective trials (particularly in primary care and rural settings) limits the ability to assess efficacy, safety, and feasibility in real-world conditions. Without region-specific data, clinicians may hesitate to adopt the protocol, and policymakers lack the evidence base needed to support its integration into national allergy management strategies. Investment in multicenter trials across Asia is urgently needed to validate outcomes and inform context-sensitive adaptations (23,30).

Cultural and Dietary Misalignment

Western ML stages typically feature foods such as muffins, pancakes, and cheese—items that are not commonly consumed in many Asian households. This cultural disconnect undermines both clinical safety and patient adherence. In regions like Indonesia, India, and Malaysia, traditional foods such as steamed rice cakes, milk-based porridges, or martabak may serve as more appropriate ladder steps, but their allergenicity and thermal processing profiles remain largely unstudied. The absence of validated, culturally adapted alternatives can lead to confusion, reduced caregiver confidence, and poor compliance. Collaborative efforts involving allergists, dietitians, and food scientists are needed to develop regionally tailored recipes with quantified milk protein content and standardized preparation methods (3,31).

Parental Anxiety and Education Deficit

Parental anxiety (particularly among caregivers of children with prior anaphylaxis) poses a significant barrier to ML initiation and progression. Studies have documented high levels of fear surrounding allergic reactions, which are often exacerbated by the lack of accessible educational materials in local languages and formats. In many Asian countries, structured guidance on ML use is limited, and clinician training is inconsistent. This educational void can result in premature discontinuation, incorrect application, or avoidance of the protocol altogether. To address this, culturally sensitive educational tools, including visual guides, mobile applications, and multilingual resources, should be developed to empower caregivers and support informed decision-making (10,23).

Healthcare Access and Monitoring Limitations

In numerous Asian regions, access to pediatric allergists, oral food challenge facilities, and emergency care remains limited. As a result, ML protocols are frequently initiated without adequate supervision or follow-up, particularly in rural or underserved communities. This lack of clinical oversight is especially concerning in IgE-mediated CMPA, where the risk of severe reactions necessitates careful monitoring. The disparity in healthcare access not only compromises patient safety but also perpetuates inequities in allergy management. Integrating ML strategies into primary care frameworks (supported by telemedicine, community health worker training, and simplified risk stratification tools) could help bridge this gap and expand safe access (22,32).

Absence of Longitudinal Outcome Data

There is a notable lack of published data on long-term outcomes following ML use in Asian children. Metrics such as sustained tolerance, nutritional recovery, growth normalization, and quality-of-life improvements remain unexplored, limiting the ability to assess the broader benefits of the protocol beyond desensitization. Without longitudinal tracking, clinicians and policymakers cannot evaluate the durability of tolerance or the cost-effectiveness of ML implementation. Establishing regional registries and cohort studies is essential to capture these outcomes and inform future guideline development. Such data would also support advocacy efforts for resource allocation and integration of ML therapy into national health systems (3,18,22).

OPTIONAL MANAGEMENT STRATEGIES FOR COW'S MILK ALLERGY IN ASIA

The management of CMPA in Asia necessitates a context-sensitive approach, given the region's heterogeneous healthcare systems, cultural dietary norms, and variable access to allergy specialists. While the ML protocol offers a structured pathway toward tolerance induction, its implementation remains inconsistent across Asian settings. Therefore, several alternative or adjunctive strategies may be considered to accommodate local constraints and optimize patient outcomes (33).

Prolonged Elimination with Nutritional Surveillance

In regions where structured reintroduction is impractical (due to limited specialist availability, caregiver apprehension, or lack of standardized protocols) extended elimination of cow's milk protein may remain the default strategy. However, this approach carries a significant risk of nutritional compromise, particularly in infants and young children during critical growth periods. To mitigate these risks, proactive nutritional surveillance is essential. This includes regular assessment of dietary intake, supplementation of calcium and vitamin D, and integration of culturally appropriate non-dairy protein sources. Collaboration with dietitians and primary care providers is crucial to ensure that prolonged avoidance does not inadvertently lead to micronutrient deficiencies or growth faltering, as emphasized by Koletzko et al. in the ESPGHAN guidelines (34) and reinforced by recent reviews on nutritional targets in CMPA management (35,36).

Early Oral Immunotherapy (OIT) in Controlled Settings

Recent studies from tertiary centers in Japan and South Korea have demonstrated the potential of low-dose OIT to accelerate tolerance acquisition in children with IgE-mediated CMPA. While OIT remains investigational in many Asian countries, its inclusion as an optional strategy may be justified in settings equipped with adequate infrastructure for risk stratification and emergency response. When initiated early under allergist supervision, OIT may serve as a viable alternative to passive elimination, particularly for families seeking proactive desensitization. Supporting this approach, the clinical outcomes and immunologic profiles summarized in Table III underscore the feasibility and safety of OIT protocols in selected Asian pediatric populations. Nonetheless, broader adoption will require standardized protocols, long-term safety data, and culturally adapted caregiver education to ensure consistent and equitable implementation (37-41).

Use of Hypoallergenic Formulas in Resource-Limited Contexts

Extensively hydrolyzed formulas (eHF) and amino acid-based formulas (AAF) continue to serve as foundational management tools for infants with moderate to severe CMPA, especially in rural or underserved areas. These formulas provide essential nutrition while minimizing allergenic exposure, thereby supporting growth and development during the elimination phase. Their use may also facilitate gradual reintroduction when tolerance is suspected, serving as a transitional medium prior to initiating ladder-based or OIT protocols. The efficacy and clinical utility of eHF and AAF have been well-documented in pediatric allergy management, with EHFs recommended for mild-to-moderate cases and AAFs reserved for severe presentations (42). However, cost and availability remain significant barriers in many Asian countries, necessitating policy-level interventions to improve access and affordability, as highlighted in regional cost-effectiveness analyses and reviews on formula accessibility (43).

Integration of Telemedicine and Community-Based Support

To bridge gaps in specialist access, telemedicine platforms may be leveraged to remotely guide families through ML or OIT protocols. This model allows for real-time monitoring, individualized adjustments, and caregiver reassurance, particularly in geographically isolated regions. Recent studies have highlighted the utility of online tools and remote consultations in supporting CMPA diagnosis and management, especially in resource-limited settings (44). Additionally, the establishment of community-based education programs, peer support networks, and culturally tailored resources can enhance protocol adherence and empower caregivers. These initiatives may also serve as referral conduits to tertiary care when escalation is warranted, as emphasized in recent regional reviews on allergy care infrastructure and caregiver engagement (2).

CLINICAL AND CULTURAL PERSPECTIVES ON THE MILK LADDER AND ORAL IMMUNOTHERAPY FOR COW'S MILK PROTEIN ALLERGY IN ASIA

Amid the rising prevalence of CMPA across Asia, the need for safe, effective, and contextually appropri-

Table III: Oral immunotherapy effect in selected studies from Asia.

First Author	Procedure / Protocol	Study Location	Success Rate (%)	Target Population	Notable Remarks
Takahashi et al. (2016) (37)	Rush OIT using microwave-heated cow's milk (MH-CM)	Japan (Osaka)	70% sustained unresponsiveness at 4 years	Children aged 5–17 years with persistent CMPA	MH-CM reduced allergenicity; safe escalation; IgE levels predictive of outcome
Takahashi et al. (2017) (38)	OIT combined with omalizumab and MH-CM	Japan (Osaka)	100% desensitization; 70% tolerated 200 mL	Children aged 6–14 years with high-risk CMPA	RCT; omalizumab improved safety; IgG4 and IgA increased; no anaphylaxis reported
Inuo et al. (2018) (39)	OIT using partially hydrolyzed formula (pHF)	Japan (Nagoya/ Yokohama)	40–65% threshold improvement; no systemic reactions	Children aged 1–9 years with IgE-mediated CMPA	Double-blind RCT; pHF safe and effective; casein-specific IgE decreased
Nagakura et al. (2020) (40)	Low-dose OIT using heated vs. unheated milk	Japan (Sagamihara)	35% (HM) vs 50% (UM) passed 3 mL OFC	Children ≥5 years with history of anaphylaxis	RCT; HM-OIT safer with fewer reactions; UM-OIT showed stronger IgG4 response to β-lactoglobulin
Maeda et al. (2021) (41)	Rush + slow OIT with fresh cow's milk	Japan (Tokyo)	50% passed 100 mL DBPCFC; 87.5% maintained >100 mL at 2 years	Children aged 3–12 years with severe CMPA (≤10 mL threshold)	RCT; significant IgE reduction; 43% required adrenaline; long-term tolerance observed

ate tolerance strategies has become increasingly urgent. Two primary approaches, ML and OIT, have emerged as promising therapeutic options, each with distinct clinical characteristics. ML offers a gradual reintroduction pathway using extensively heated milk-containing foods, with low risk and potential for home-based implementation. In contrast, OIT involves the administration of measured milk doses in a clinical setting, requiring close supervision and aiming for more aggressive desensitization (6).

In the Asian context, where access to allergy specialists remains limited and dietary patterns are heavily influenced by cultural norms, comparing ML and OIT is not only relevant but essential. ML demonstrates advantages in flexibility, affordability, and cultural compatibility, yet faces challenges in validating locally adapted recipes and standardizing protein dosage (3). Meanwhile, OIT has been evaluated in tertiary centers in Japan and Korea, showing promising outcomes in accelerating tolerance among patients with IgE-mediated CMPA. A retrospective study by Matsumoto et al. indicates that ML and OIT yield comparable effectiveness in achieving milk tolerance, though ML is more accessible and acceptable to families in resource-limited settings (12).

Table IV presents a comprehensive comparison between ML and OIT, highlighting clinical considerations, risk stratification, cultural relevance, and potential integration into Asian healthcare systems (12,16-18,37-41). With evidence-based design and appropriate local adaptation, ML holds promise as a more inclusive and sustainable tolerance strategy, particularly in regions with limited infrastructure. However, for high-risk cases, OIT remains a viable option when adequate facilities and trained personnel are available. Further comparative studies are needed to strengthen the scientific foundation and support the development of regionally contextualized and safe clinical guidelines (3,6,12).

CONCLUSION

Tolerance strategies for CMPA in Asia require adaptive, evidence-based approaches. ML and OIT represent two distinct intervention pathways, differing in methodology and operational demands. ML is more suitable for populations with limited access to specialized care and culturally specific dietary preferences, whereas OIT has demonstrated high efficacy in IgE-mediated cases within tertiary care settings. However, challenges related to recipe vali-

Table IV: Approaches to CMPA management: Milk ladder vs. oral immunotherapy in Asia

Aspect	Milk Ladder	Oral Immunotherapy (OIT)
Primary Objective	Gradual reintroduction of milk protein through thermally processed foods	Active desensitization via controlled exposure to milk protein
Target Population	Typically suitable for non-IgE-mediated CMPA and mild-to-moderate IgE cases	Primarily indicated for moderate-to-severe IgE-mediated CMPA, including anaphylaxis
Implementation Setting	Home-based with adequate caregiver education	Conducted in clinical settings under close medical supervision
Safety Profile	Relatively safe for low-risk cases; risk increases without standardized local protocols	Requires risk stratification and readiness to manage severe allergic reactions
Cultural Adaptation	Highly dependent on locally available foods (e.g., steamed sponge cake, dorayaki, hotteok)	Clinically adaptable but less integrated with traditional dietary practices
Education & Adherence	Requires culturally tailored visual aids and language support for caregiver confidence	Demands intensive education and psychological support, especially for families with prior severe reactions
Status in Asia	Not yet standardized; informal adaptations observed in select countries (e.g., Indonesia, Korea)	Limited clinical trials in Japan and Korea; protocols remain investigational
Clinical Effectiveness	Effective in accelerating tolerance in mild CMPA cases	Demonstrates increased IgG4 and decreased IgE levels; higher potential for sustained tolerance
Advantages	Accessible, low-cost, and adaptable to local food practices	Greater potential for full desensitization; suitable for high-risk cases
Limitations	Unsuitable for severe CMPA; elevated risk without clinical oversight	High cost, limited availability, and requires specialized infrastructure and personnel

dation, caregiver education, and healthcare infrastructure necessitate rigorous comparative evaluation. Considering clinical, cultural, and logistical factors, ML currently holds greater advantages in terms of affordability and potential for widespread implementation across Asia, although OIT remains relevant for high-risk cases. The development of regionally tailored guidelines and multicenter studies is essential to ensure the safety, efficacy, and sustainability of both approaches within diverse healthcare systems.

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Conflict of Interest

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