PICO #3- Pediatrics

Summary: 9 y/o female brought in by mom for physical exam for school with paperwork, also reporting lesions to right temple/hair line for approximately one month. On exam patient with six dome-shaped flesh-colored papules with a central depression to right hairline and temple region without surrounding erythema. Patient with presumed Molluscum Contagiosum. Counseled mother that lesions will self resolve within 6-18 months and provided dermatology referral for discuss possible treatment options.

Search Question: In pediatric patients with molluscum contagiosum, does active treatment compared with placebo or observation improve lesion clearance, prevention of lesion spread, and treatment-related adverse effects?

Question Type:

☐ Prevalence
☐ Screening
☐ Diagnosis
☐ Prognosis
☐ Treatment
☐ Harms

The highest level of evidence to answer this question is a systematic review or meta-analysis. However, randomized controlled trials can also be very useful as these are the next highest level of evidence evaluating treatment effectiveness. In addition, cohort studies or case control studies may also be considered, as they can provide useful observational data on treatment outcomes and safety.

PICO Search Terms

P	I	C	O
Molluscum Contagiosum	Treatment	Placebo	Clearance
Child	Therapy	Observation	Resolution
Infant	Topical	Watchful waiting	Spread

Adolescent	Berdazimer	No treatment	Transmission
Pediatric	Cantharidin	Self resolution	Lesion count
	Cryotherapy		Adverse effects
	Currettage		

Search tools and strategy used:
Please indicate what databases/tools you used
Provide a list of the terms you searched together in each tool
How many articles were returned using those terms and filters.
Explain how you narrowed your choices to the few selected articles.

For example, if your search returned 25 articles among the several databases used, what was the process used to determine which four articles to use?

PubMed:
Search term:
("Molluscum Contagiosum"[Mesh] OR "molluscum contagiosum"[tiab]) AND ("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR pediatric) AND (treatment OR therapy OR topical OR cryotherapy OR curettage OR cantharidin OR berdazimer) AND (placebo OR control OR observation OR "watchful waiting" OR "no treatment" OR self resolution) AND (clearance OR resolution OR "lesion count" OR spread OR transmission OR adverse effects)

Initial result: 149 articles:
With filters: 100 articles (past 10 years and published journal articles.

Cochrane Library:
Search term:
molluscum contagiosum AND child* AND treatment

I found that when I complicated the search term, it continuously yielded no results.
Initial results found: 5 reviews
With filters: 3 reviews

I ultimately decided to use 3 articles found from PubMed. I decided to prioritize systematic review and meta-analysis over other study types. I also wanted articles that directly tested treatment vs placebo. The titles were screened for relevance, followed by reading the abstract. The three articles selected were the strongest level of evidence that directly addressed my PICO. Although, one article from PubMed was a Cochrane

review that did not appear on the Cochrane library making me think that perhaps I need to familiarize myself better with how to search on Cochrane library.

Results found

1. Oganesyan, A., Sivesind, T. E., & Dellavalle, R. (2023). From the Cochrane Library: Interventions for Cutaneous Molluscum Contagiosum. *JMIR dermatology*, *6*, e41514. https://pmc.ncbi.nlm.nih.gov/articles/PMC10335125/

Abstract:

Molluscum contagiosum (MC) is a cutaneous and mucosal condition that primarily affects children and immunocompromised adults. It presents with skin-colored, dome-shaped papules on the skin and may be associated with pain, pruritus, erythema, and, rarely, bacterial superinfection. Although spontaneous resolution generally occurs, treatment may be indicated for cosmetic purposes or to prevent spread.

A 2017 Cochrane systematic review [1] evaluated 22 randomized controlled trials (N=1650 participants, aged 0-36 years) and sought to provide an evidence base supporting specific treatments. Inclusion criteria required participants to have a clinical diagnosis of MC, excluding those with immune deficiency or sexually transmitted MC, as well as assessment of physical ablative methods (curettage, cryotherapy), topical agents (potassium hydroxide, iodine, trichloroacetic acid, salicylic acid, 10% phenol/70% alcohol, tretinoin, oils, cantharidin, podophyllotoxin, imiquimod), and systemic therapy (cimetidine, 35 mg/kg per day; calcarea carbonica, daily for 15 days).

The primary outcome was short-term clinical cure, defined as the complete disappearance of lesions up to 3 months after the initiation of treatment, as assessed by a physician. The secondary outcomes were clinical cure up to and beyond 6 months, time to cure, recurrences (after 3, 6, and 12 months), adverse effects (pain, blistering, sensitization, scarring, erosion, and pigmentary changes), spread, and disease-related quality of life.

The treatment comparisons performed in the included studies are summarized in Table 1. Data from this review strongly support awaiting spontaneous resolution of molluscum lesions and demonstrated that 5% imiquimod was no more effective in terms of clinical cure than the placebo (with an identical vehicle). Furthermore, the use of 5% imiquimod was reported to be more harmful regarding application site reactions and no more effective than its vehicle over a 3-month period.

Key Points:

- Cochrane systematic review summarizing 22 RCTs on interventions for molluscum contagiosum including topical treatment and procedural therapies compared with placebo or observation.
- Measured outcomes included lesions clearance, lesion count reduction, time to resolution, and adverse effects.

- Results: evidence for many treatments are limited and inconsistent, though cryotherapy showed some benefit in a small trial

Selection Explanation: This systematic review, one of the highest levels of evidence, addresses my PICO as it synthesizes the best available evidence across multiple trials regarding treatment vs watchful waiting of molluscum contagiosum. Although it doesn't solely focus on pediatrics, it does use pediatric studies, and addresses many of the outcomes my PICO sought to explore. Some limitations include heterogeneity of study designs, small sample sizes, and some risk of bias in individual trials but it provides a strong, high-level overview of treatment effectiveness and safety.

2. Pera Calvi, I., R Marques, I., Cruz, S. A., Mesquita, Y. L. L., Padrao, E. M. H., Souza, R. M., Brown, A., Caçador, D. G. V., Poppe, L. M., & Lopes Almeida Gomes, L. (2023). Safety and efficacy of topical nitric oxide-releasing berdazimer gel for molluscum contagiosum clearance: A systematic review and meta-analysis of randomized controlled trials. *Pediatric dermatology*, *40*(6), 1060–1063. https://pubmed.ncbi.nlm.nih.gov/37721050/

Abstract: Molluscum contagiosum (MC) is a contagious infection that, although benign, can become an aesthetic burden and lead to other opportunistic infections, secondary dermatitis, and self-isolation. Currently, several treatment options are available for MC, including the newly investigated nitric oxide-releasing berdazimer gel, leading this review to evaluate randomized controlled trials (RCT) comparing berdazimer gel with a vehicle for treating MC. The meta-analysis included three reports and four RCT involving 1854 patients, with 1106 (59.6%) randomized to receive berdazimer. Our findings suggest that berdazimer is effective in the management of MC lesions, but the increased clearance of lesions and reduction of scarring must be weighed against the potential for topical adverse effects, particularly when considering the use of this therapy in pediatric patients.

Key Points:

- Systematic review/meta-analysis (multinational, including the United States) of randomized control trials with 1,854 particpatnts, including pediatric patients, evaluating topical berdazimer gel vs placebo.
- Measured outcomes included complete lesions clearance, reduction in lesion count, and treatment-related adverse effects.
- Results: significantly higher rates of complete lesion clearance and greater reduction in lesion count with berdazimer gel compared to placebo.

Selection Explanation: This systematic review, one of the highest levels of evidence, provides high-level of evidence by synthesizing results from multiple randomized control trials. It directly addresses my PICO by comparing treatment vs no active treatment for molluscum contagiosum.

3. Browning, J. C., Enloe, C., Cartwright, M., Hebert, A., Paller, A. S., Hebert, D., Kowalewski, E. K., & Maeda-Chubachi, T. (2022). Efficacy and Safety of Topical Nitric Oxide-Releasing Berdazimer Gel in Patients With Molluscum Contagiosum: A Phase 3 Randomized Clinical Trial. *JAMA dermatology*, *158*(8), 871–878. https://pmc.ncbi.nlm.nih.gov/articles/PMC9280611/

Abstract:

Importance: Molluscum contagiosum (MC) is a highly contagious skin condition. Lesions may persist for months to years, and no US Food and Drug Administration–approved medications are currently available in the US.

Objective: To assess the efficacy and safety of berdazimer gel, 10.3%, a novel topical nitric oxide–releasing medication, in the treatment of MC.

Design, Setting, and Participants: This was a multicenter, vehicle-controlled, double-blind, phase 3 randomized clinical trial (B-SIMPLE4) conducted in 55 clinics (mostly dermatology and pediatric) in the US from September 1, 2020, to July 21, 2021. Eligible participants were 6 months or older and had from 3 to 70 raised MC lesions. Patients with sexually transmitted MC or with MC only in the periocular area were excluded.

Interventions: Patients were randomized to treatment with berdazimer gel, 10.3%, or vehicle gel, applied as a thin layer to all lesions once daily for 12 weeks.

Main Outcomes and Measures: The primary efficacy end point was complete clearance of all MC lesions at week 12. Safety and tolerability measures included adverse event frequency and severity, and assessment of local skin reactions and scarring. Data analyses were performed from August 31, 2021, to September 14, 2021.

Results: A total of 891 participants were randomized, 444 to berdazimer, 10.3% (mean [range] age, 6.6 [0.9-47.5] years; 228 [51.4%] male; 387 [87.2%] White individuals), and 447 to vehicle (mean [range] age, 6.5 [1.3-49.0] years; 234 [52.3%] female; 382 [85.5%] White individuals). In the intention-to-treat population, 88.5% (393 patients) in the berdazimer group and 88.8% (397 patients) in the vehicle group had a lesion count performed at week 12. At week 12, 32.4% (144 patients) in the berdazimer group achieved complete clearance of MC lesions compared with 19.7% (88 patients) in the vehicle group (absolute difference, 12.7%; odds ratio, 2.0; 95% CI, 1.5-2.8; $P < .001$) with 14.4%

(64 patients) of the berdazimer group discontinuing treatment because of MC clearance compared with 8.9% (40 patients) of the vehicle group. Adverse event rates were low. The most common adverse events were application-site pain and erythema, mostly mild in severity. Adverse events leading to discontinuation affected 4.1% (18 patients) of the berdazimer group and 0.7% (3 patients) of the vehicle group. The most common local skin reaction was mild to moderate erythema.

Conclusions and Relevance: Use of berdazimer gel, 10.3%, for MC appears to demonstrate favorable efficacy and safety with low adverse event rates.

Key Points

- Phase 3 randomized, double blinded clinical trial evaluating the efficacy and safety of topical berdazimer gel vs placebo with over 800 participants aged 2 and older, the majority of whom were pediatric patients.
- Measured outcomes included complete lesion clearance, reduction in lesion count, and treatment-related adverse events.
- Results: 32.4 of patients in the berdazimer group achieved complete lesion clearance compared to 19.7% in the placebo group, showing significant benefits of treatment

Selection Explanation: This randomized clinical trial directly addressed by PICO by comparing active treatment with placebo and it included a large pediatric population. There are potential bias, including sponsorship bias, but the rigorous randomized, double blind study design helps to offset this bias.

Clinical Bottom Line:

Evidence from systematic reviews, meta-analysis, and randomized clinical trials suggest that active treatment for molluscum contagiosum can improve lesion clearance compared to self-resolution. The phase 3 randomized clinical trial demonstrated significantly higher lesion clearance. Similarly, the meta-analysis by Calvi et al. found improved clearance rates as well. However, the Cochrane systematic review found that evidence for treatment remains limited or inconsistent. Therefore, watchful waiting is often an appropriate first-line management strategy and those with extensive lesions, symptoms, or psychosocial concerns may benefit most from treatment. Treatment may accelerate lesion resolution, but clinicians should weigh the benefits against potential mild local adverse effects of topical treatment.