






# Therapeutic approaches to Condyloma Acuminatum in children and adolescents

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## ABSTRACT

**Objectives:** Infection with human papillomavirus types 6 and 11 can progress to Condyloma acuminata. Its transmission is mainly sexual, so these warts in children should be considered an alarm signal for abuse investigation. Eventually, however, it occurs by autoinoculation or fomites. Treatment is challenging, given that despite the extensive arsenal, recurrence is common. The present systematic review compares the success rates of therapeutic strategies, aiming to provide a substrate for the right choice in the treatment of the disease in children and adolescents. **Methods:** A systematic review was performed based on the guideline for *Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA)*, registered on the PROSPERO Platform under identification CRD42021262090. **Results:** 211 studies were found in the databases consulted, and 30 met the proposed criteria established in the systematic research. These passed data extraction for qualitative synthesis, demonstrating the effectiveness of non-invasive to invasive methods. **Conclusions:** Due to good results in disease resolution and reduced adverse effects, the most popular therapy among the authors was Imiquimod. The research called attention to the need for more robust studies and more complex methodologies about the therapeutic approaches of Condyloma Acuminatum in children and adolescents.

**Keywords:** Condyloma acuminatum, Papillomavirus infections, Imiquimod.

## INTRODUCTION

The human papillomavirus, HPV, through its different types, can cause transient or persistent infection of the genital tract epithelium; it can be oncogenic or non-oncogenic. The infection may be subclinical, detected by molecular methods or cytology, or clinically manifested as a condyloma or neoplasm<sup>1</sup>.

Condylomatous manifestation is mainly caused by HPV types 6 and 11.<sup>2,3</sup> Its evolution starts with the appearance of moist and soft papules, skin-colored or hyperpigmented with millimeters in diameter. Developing over weeks to months, the initial lesions can agglutinate, forming plaques or white, exophytic, and papillomatous growth with a “cauliflower” appearance<sup>2</sup>.

In males, condylomata acuminata are most commonly detected in the perianal area, while in females, the presentation can be in the perianal, perineal, vulva, vaginal vestibule, or per urethral areas, as well as on mucosal surfaces of the vagina, rectum, or oropharynx. Although the lesions are occasionally itchy or painful, they are

usually asymptomatic and bleeding rarely occurs. Regarding detection, large lesions can be seen with the naked eye, but a colposcopy is necessary to identify smaller lesions<sup>3</sup>.

As for epidemiology, human papillomavirus infection is the most common sexually transmitted infection in the world<sup>4,3</sup>. However, epidemiological data on condyloma acuminatum in children are limited and the prevalence in this population is unknown. It is estimated that the average age of children with condyloma acuminata varies between 2.8 and 5.6 years<sup>5</sup>, and the predominance of females is suggested by several studies<sup>6,3</sup>.

Despite the high prevalence of genital HPV infection, vertical transmission, in addition to colonization, transient skin damage is rare. Despite this, conjunctival, laryngeal, vulvar, or perianal lesions present at birth or that appear early probably result from perinatal exposure to maternal HPV. The infection, however, is not related to the presence of maternal genital warts or to the route of delivery and for this reason, cesarean section is generally not indicated for maternal HPV infection, except in cases of bulky genital lesions

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that may obstruct the mode of delivery or suffer avulsion and bleeding with dilation of the uterine cervix or during vaginal delivery<sup>7</sup>.

Condyloma acuminata can also develop as a result of acquiring the HPV infection by other non-sexual means since transmission by autoinoculation or fomites seems to be possible<sup>7</sup>.

Through heteroinoculation, the transmission of HPV can occur during non-sexual contact with a caregiver, such as bathing or changing diapers, and through self-inoculation, children can acquire anogenital lesions due to contact with the virus from other cutaneous or mucosal sites of infection<sup>3</sup>.

The presence of genital warts in children after infancy is always a reason to consider the possibility of sexual abuse<sup>7</sup>, and suspicion should increase as the child gets older<sup>8</sup>.

In terms of case resolution, few data are available on condyloma acuminatum in children, but it has been shown that many infections resolve spontaneously<sup>3</sup>.

However, several therapies have been used to treat condyloma acuminatum in adults and children. They consist of interventions that mechanically or chemically remove infected tissue, or that upregulate the host's immune response against virus-infected cells<sup>3</sup>.

Although these treatments can eradicate the lesions, recurrence of the disease is common. Although it varies greatly according to the choice of therapy, it is known that it occurs on average in 20 to 30% of patients in general<sup>3,8</sup>, and that it imposes the need for repeated medical consultations and treatment<sup>9</sup>.

Therefore, considering the biopsychosocial implications of condyloma acuminatum in childhood, as well as the high recurrence statistics, the different therapeutic options, together with their varied success rates, the present systematic review aims to compare and understand the best treatment strategies to guide therapeutic decision-making.

## METHODOLOGY

### Kind of study

A systematic review based on the guideline for *Preferred Report Items for Systematic*

*Reviews and Meta-Analyses* (PRISMA), registered on the PROSPERO Platform under identification CRD42021262090.

### Eligibility Criteria

The inclusion criteria were: 1) Case-Control, Cohort, Case Report, and Case Series Studies; 2) that included treatment of condyloma acuminatum in children and adolescents up to 18 years. There was no language restriction, and articles published between 2010 and 2021 were included. Studies were excluded for the following reasons: articles in which the main subject was not Condyloma acuminata; or that did not address the pathology in children or adolescents; or that did not explain the therapy used; or case reports with associated Buschke-Lowenstein tumor.

### Database and Search Strategy

The present systematic review deals with the treatment of condyloma acuminatum in children and adolescents up to 18 years. To systematize the research, the PRISMA recommendation was used. PubMed/*Medical Literature* databases were used for the study. *Analysis and Retrieval System Online* (MEDLINE), and Latin American and Caribbean Literature on Health Sciences (Lilacs). Data collection was carried out from February to April 2021. In addition, a manual search was performed to find possible articles not included in the databases. The research was based on the MeSH and DeCS descriptors " *Condylomata acuminata*", " *Child*" and " *Treatment* " along with the boolean operators AND and OR , resulting in the combination " *Condylomata acuminata*" AND (" *Child* " OR " *Infant* ") AND " *Treatment* ".

### Selection of studies

The selection was based on phases. In phase 1, eligibility was analyzed by screening performed by reading the title and abstract by a pair of reviewers independently. In phase 2, confirmation of eligibility was performed with

the full reading of the works by the same pair of reviewers independently, excluding works that did not meet the eligibility criteria established above.

## Data collect

When present, the following variables were extracted: title, authors, year, and type of publication, sample size, age of patient-cases, site of injury, the method used for diagnosis, treatment performed, adverse effects of treatment, concomitant with other sexually transmitted infections, whether the lesions were due to sexual abuse, relapse, and follow-up time to prepare the review, in addition to observations, where appropriate.

## Summary of measures

The primary outcome of interest in the systematic review was the type of therapy used.

In addition, treatment efficacy and adverse effects, as well as whether anesthesia was used.

## RESULTS

### Selection of Studies

211 studies were found in the databases consulted, 199 PubMed /MEDLINE, and 12 Lilacs, according to the search criteria explained above. After a detailed analysis of the works, 179 were excluded for not meeting the eligibility criteria. The remaining 32 had the duplicates removed, leaving 30 publications. In the end, these works were selected for data extraction and qualitative synthesis.

### Characteristics of the Studies

Of the 29 selected studies, 20 consisted of a case report, while seven case series, a review, and a descriptive study. The characteristics of each are summarized in Table 1.

**Table 1**

Use of treatments for condyloma acuminatum in children and adolescents in the literature from 2010 to 2021.

	AUTHOR AND YEAR	DRAWING	SAMPLE	AGE	LOCATION OF INJURY	TREATMENT	IT IS MADE ADVERSE	RECURRENCE	FOLLOW UP
1	Giancristoforo et al., 2020	Case report	1	2 years	Vulvar and perianal	Imiquimod 5%	No	No	2 years
2	Muffarrej et al., 2020	Case report	1	9 years old	-	Topical cidofovir	No	No	6 months
3	He et al., 2020	Case report	1	2.5 years	Perianal	Hyperthermia	Itching	No	Four months
4	Drumond et al., 2019	Case report	1	9 months	Vulvar	Imiquimod 5%	No	No	-
5	Chamseddin et al., 2019	Revision	37	< 12 years	Anogenital	17: imiquimod 5% 9: sinecatechin ointment 15% 12: combined	Imiquimod : Milderythema	2 cases	-
6	Hernández et al., 2019	Descriptive study	33	<18 years	Genitals	Topical and systemic homeopathic (Cinnabaris-mercurius sulphuratus ruber; Euphrasia ; nitricum acidum; Sabine; Thuya occidentalis; staphysagria )	No	3 cases	4 years
7	Garaix et al., 2018	Case report	1	11 years	Anal	Electrocoagulation	-	-	6 years
8	MeiNian et al., 2018	Case series	12	1 to 4 years	Perianal and perineal	Photodynamic therapy (PDT) and 5-ALA 20%	Local pain	No	6 months
9	Veasey et al., 2017	Case series	20	<12 years	70% perineal	13: Podophyllin 20% and Imiquimod cream 5% 7: Topical and surgical			4 years
10	Akpadjan et al., 2017	Case report	1	2 years	Vulvar and perianal	Surgical excision and electrocoagulation	No	Yea	1 year and 6 months
11	Godoy- Gijon et al., 2017	Case report	1	7 years	Perianal and perineal	Sinacatechin ointment	No	No	1 year

(Continuação)

**Table 1**

(Continuação)

	AUTHOR AND YEAR	DRAWING	SAMPLE	AGE	LOCATION OF INJURY	TREATMENT	IT IS MADE ADVERSE	RECURRENCE	FOLLOW UP
12	Rob et al., 2017	Case report	1	11 years	Perianal	Sinecatechin ointment	No	No	12 weeks
13	Calderón -Castrat et al., 2016	Case report	1	2 years	Periurethral and perianal	CO2 laser	-	No	13 months
14	Patel et al., 2014	Case report	1	3 years	Periurethral and vulvar	Excisional biopsy	-	No	9 months
15	Percinoto et al., 2014	Case report	1	5 years	Tongue and palate	Excisional biopsy	-	No	30 days
16	Dugić et al., 2014	Case report	1	1 year		Imiquimod 5%	perilesional burn	No	18 months
17	Varma et al., 2013	Case report	1	9 years old	Perianal	Ata 80%	-	-	-
18	Smith et al., 2013	Case series	4	4/5/6/7 years	-	Imiquimod 5%	Psoriasisform eruption and ulceration in oral mucosa	-	-
19	Leclair et al., 2012	Case report	1	3 years	Perianal	Imiquimod 5%	-	No	24 months
20	Fernández -Morano et al., 2012	Case series	2	56 years	Perianal	Cidofovir 1%	Irritation	No	2 and 3 months
21	Stefanaki et al., 2012	Case series	38	1/ 11 years	Perianal	16: podophyllotoxin 6: imiquimod 5% 6: cryotherapy 10: combined	-	No	3 months
22	Rodrigues et al., 2011	Case report	1	3 years	Perianal	Imiquimod 5%	Moderate erythema and fissures <i>minor</i>	No	1 year
23	Masuko et al., 2011	Case report	1	2 years	Perianal and perineal	Imiquimod 5%	moderate erythema	No	3 months
24	Val et al., 2011	Case series	3	1/4/4 years	Genitals	Imiquimod 5%.	Self-limited fever and hyperemia in 1 case	No	1 year
25	Chatterjee et al., 2011	Case report	1	2.5 years	Perianal and perivulvar	-	-	-	-
26	Güçer et al., 2011	Case report	1	1 year	Perianal	Surgical excision	Small suture dehiscence	-	-
27	Chen et al., 2010	Case report	1	9 years old	Vulvar	Aminolevulinic Acid 5% and PDT	Mild pain and swelling of labia minora	No	6 months
28	Brandt et al., 2010	Case series	4	1/1/2/2 years	Perianal and perineal	Imiquimod 5%	Erythema in 1 case	No	6 months
29	Skowrona et al., 2010	Case report	1	2 months	Perianal and inguinal	Imiquimod 5%	Mild erythema and ulcers	No	6 months

## Imiquimod

Imiquimod 5% is an immune response modifier, activating immune cells through agonism with *Toll-like* receptor 7. Its topical application to the skin is associated with increases in cytokines and immune system cells. Its use consists of applying a thin layer of the 5% cream three times

a week before going to bed, on alternate days so that the product remains on the skin for about 6 to 10 hours. It must be removed later with water and neutral soap. Treatment should be continued until the warts are completely eliminated or for up to 16 weeks. The most predominant adjacent effects are mainly dermatological, such as erythema, phlogosis, pruritus, and xeroderma<sup>10</sup>.

Thirteen studies used this therapeutic strategy, twelve of them in monotherapy. The response to treatment was satisfactory in most patients, with few reports of adverse effects, which were mostly mild<sup>6,11-22</sup>.

## Sinecatechins

The mechanism by which Sinecatechins ointment helps eliminate genital and perianal warts is uncertain since its antioxidant properties were observed *in vitro* without the actual mechanism being known *in vivo*. Guidelines for pediatric use are not included in the medication package insert, so for adults, a thin layer of ointment should also be manually applied to the lesions externally, and it is not recommended to apply it to open wounds or use a dressing. Among its adverse effects, those that stand out in terms of frequency are similar to those of Imiquimod, ranging from erythema, itching, burning sensation, edema, and local pain<sup>23</sup>.

Two authors used Sinecatechin ointment and in both case reports, the therapy was adequate to eliminate the lesion<sup>24,25</sup>.

## Podophyllin

The also topical strategy Podophyllin Resin, in turn, acts by interrupting the division of the lesion cells, in the mitosis phase, through the binding to a protein subunit of the spindle microtubules, the tubulin. In such a way, the drug acts directly on the metabolism of the epithelial cell, being, therefore, a keratolytic agent. The applicator supplied with the product must be used to apply the product moderately to the lesions, avoiding contact with healthy tissue, allowing them to dry completely. In the first application, it is recommended to leave it for about 30 to 40 minutes to determine the patient's sensitivity and in subsequent applications, let it act for 1 to 4 hours, depending on the severity of the injury, and the drug should be removed with alcohol or soap and water once the treatment time has elapsed. Incorrect application of the drug can lead to systemic absorption, inducing fever,

leukopenia, thrombocytopenia to paralytic ileus, polyneuropathy, and coma. That said, it must be carefully indicated<sup>26</sup>.

Podophyllin was used in 16 patients with resolution of the conditions<sup>6</sup>. It was also studied in association with Imiquimod 5% in 13 patients, showing a satisfactory response<sup>14</sup>.

## Trichloroacetic acid

Trichloroacetic acid, another keratolytic approach, in turn, denatures proteins in the epidermis, leading to ischemic necrosis, manifested by whitening of the area, in addition to changes in skin elasticity. It must be applied by a healthcare professional and, if necessary, can be repeated weekly. The professional must be careful to avoid applying excessive amounts and exposing the surrounding tissue to the drug. As one of the effects can be severe pain after application or excessive tissue exposure, sodium bicarbonate, liquid soap, or talc can be effective neutralizers that help to remove the remaining product<sup>3,27</sup>. This topical drug alternative appeared in a case report<sup>28</sup> with good evolution.

## Cidofovir

Cidofovir is a nucleotide monophosphate analog and works by competitively inhibiting the incorporation of deoxycytidine triphosphate into viral DNA so that the drug stops chain elongation. Thus, it demonstrates *in vitro* activity against several viruses, but clinical efficacy has been studied and demonstrated only against Cytomegalovirus<sup>29</sup>.

One study<sup>28</sup> used therapy in an immunosuppressed patient, and another<sup>31</sup> used topical Cidofovir in two patients so that all of them showed the disappearance of the lesions.

## Cryotherapy

Cryoablation with liquid nitrogen or nitrous oxide destroys wart tissue through cell lysis. Although it is an outpatient procedure, cryoablation causes pain during application and,

subsequently, variable localized inflammation. Providing local anesthesia for the procedure is especially important when the area to be subjected to cryotherapy is extensive<sup>3,27</sup>.

In a series of cases, six patients submitted to cryotherapy had resolution of the lesions<sup>6</sup>.

## Laser

Lasers produce light energy, which is absorbed by water in warty tissues, causing thermal damage and resulting in ablation. The carbon dioxide laser is the most commonly used type of laser for treating vulvar warts. It requires specific training and specialized equipment, as one of the risks of the technique is exposure to pulverized HPV DNA. Its main adverse effect is related to the formation of scars at the lesion site<sup>3,27</sup>.

Among the procedures, the CO<sub>2</sub> laser was used in one patient, and it was effective<sup>32</sup>. Photodynamic Therapy (PDT) appeared in association with Aminolevulinic Acid in a series and a case report, in which all patients showed a good response to treatment<sup>33,34</sup>.

## Electrocoagulation

Electrocautery can also be used for the ablation of vulvar and vaginal lesions. The advantage of this approach over cryoablation is that a single session has a greater ability to eliminate warts. However, it requires anesthesia, and that is performed in a surgical center. If available, laser ablation is generally preferred because it is associated with less bleeding and discomfort after the procedure, which are more common effects after electrocoagulation<sup>3,27</sup>.

A case report showed the resolution of the condition when electrocoagulation was used<sup>35</sup>. Another study associated this modality with surgery, which, however, underwent a recurrence, being definitively resolved with a new session with electrocautery<sup>36</sup>.

## Excision

As stated, surgical excision can be performed given the possible need for tissue for histological

diagnosis; in this case, an excisional biopsy before an ablative procedure or even an excisional procedure can be performed only for therapeutic purposes. Typically, exophytic lesions are excised to the level of normal skin using scissors or a scalpel and the base of the lesion is cauterized. For larger lesions, wide local excision is often required. Tangent to adversities, patients may experience pain, dyspareunia, scar formation or infection<sup>3,25</sup>.

Two reported cases underwent excisional biopsy, with a satisfactory response to treatment<sup>37,38</sup>. One study addressed a giant condyloma acuminatum with surgical excision, with therapeutic success<sup>39</sup>.

## DISCUSSION

This review consists of 29 articles on the different therapies against condyloma acuminatum in children and adolescents up to 18 years, which were published between 2010 and 2021. The small number of studies with a judicious methodology was perceived as a limitation of the study, given that most of them are case reports. And among them, the follow-up time, which ranged from 12 weeks to six years, can lead to a misinterpretation of one or another treatment. A favorable outcome was considered to be the involution and elimination of the lesion and the presence or absence of recurrence.

There are several therapies to treat condyloma acuminatum in children and adults, so the responses to the approaches vary and can be resolved with expectant management. Associated with the great influence of pain tolerance, non-intervention is frequently used for the management of condyloma acuminatum in children<sup>40</sup>. However, it is preferable to approach the wart if there are symptoms, such as itching, bleeding or pain, or when the lesions can cause emotional distress to the child or are socially harmful. Furthermore, lesions that persist for more than two years are less likely to resolve spontaneously<sup>5</sup>.

Despite the various forms of intervention, there is currently no standard gold treatment that is consistently effective or has been studied in large clinical trials with children. Thus, the recurrence of lesions is frequently seen<sup>5</sup>. The proposed therapies mainly consist of interventions that



mechanically or chemically destroy infected tissue or that upregulate the host's immune response against infected cells. Since these methods may depend on patient compliance and pain threshold, anesthesia may be required<sup>21</sup>. In addition, the home application of topical medications gives rise to non-adherence to treatment, which may be the reason for recurrent conditions<sup>22,39</sup>.

Among the major recommendations of these classes found in the literature, mostly in adults, we can mention Imiquimod 5% and Podophyllin 0.5%<sup>3,27</sup>. These two approaches have been shown to have a similar effect on anogenital warts by comparison, and are also associated with identical and acceptable side effects. Both substances, in immunocompetent subjects, have been shown to be effective and safe for untreated anogenital warts in individuals<sup>41</sup>.

The findings of the current review corroborate the literature regarding the treatment of condyloma acuminatum in general since thirteen were the studies that used Imiquimod as a therapeutic alternative<sup>6,11-22</sup>. However, the FDA, Food and Drug Administration provides information that both the safety and efficacy of the cream in children under 12 years of age for the treatment of genital and perianal warts are unknown, and therefore it is not officially recommended for this public<sup>42</sup>.

Despite this scarcity of data and official recommendations, most of the patients studied showed a good response to treatment, with the resolution of the condylomatous lesion in patients aged between 2 months and 12 years. Of those with some adverse effect, mild to moderate local erythema was cited, one patient had a minor fissure and another had a perilesional burn. One of the case series showed rarer and more pronounced effects, such as a psoriasiform eruption and ulcer on the oral mucosa<sup>15</sup>.

Podophyllin is also similar to Imiquimod in that despite being effective for condyloma acuminatum, supported by large studies in adults<sup>43-44</sup>, data on efficacy and safety in children are still scarce. Among the active ingredients, a study showed that 0.5% podophyllotoxin solution was superior to 25% liquid podophyllin in eliminating all warts<sup>42</sup>. The series with 16 cases using podophyllotoxin reinforces this finding once

the lesions resolved. However, the use of 20% podophyllin in association with Imiquimod was also effective in 13 patients in another study. Although high rates of recurrence have been reported with discontinuation of treatment<sup>45</sup>, the cases studied did not progress to recurrence. There were also no manifestations of unwanted effects in the patients.

Topical Cidofovir, despite not being formally recommended for condyloma acuminatum, was used in two studies<sup>30,31</sup>. In one of them, Cidofovir Cream 1% was used on the lesions of a nine-year-old patient daily<sup>30</sup>, while in the other the same percentage was used in two patients, five and six years old, but in one using it once a day, and in the second, twice a day<sup>31</sup>, for varying durations according to the response to therapy. The most pronounced adverse effect was local irritation, but the therapy proved to be effective in resolving warts. This finding corroborates previous case reports, which also demonstrated complete and permanent remission of these anogenital lesions with topical, intralesional or systemic administration of cidofovir<sup>3</sup>. However, this therapy still lacks a large controlled trial to assess its efficacy and effects.

Further on, as postulated in the literature, more invasive procedures such as cryotherapy, electrodesiccation, and surgical and laser excision are generally reserved for patients with extensive warts or who are resistant to topical therapy<sup>3</sup>.

Laser ablation is preferred for extensive or multifocal lesions when large areas of vulvar skin, for example, would have to be removed if an excisional approach. Despite the scarcity of data on recurrence after the intervention, a study showed a recurrence rate of 17% in the group of patients treated with laser therapy<sup>46</sup>. However, in the present review, no patient presented a recurrence of the condition. Although the technique is related to less discomfort<sup>3,27</sup>, to perform the procedures, the children were submitted to anesthesia<sup>32,33</sup>. In case series<sup>33</sup>, Chloral Hydrate was used for sedation, while in the report<sup>32</sup>, the patient was submitted to general anesthesia and antibiotic prophylaxis with Cefazolin. As a treatment effect in some patients, local pain and mild swelling were observed.

Cryoablation, which is also related to post-procedure local pain and inflammation in the

literature<sup>3,27</sup>, did not generate any adverse effects in the sampling of six patients in a series of cases and also did not present recurrence.

Electrocautery is superior to cryoablation in terms of the number of sessions since a single session is usually sufficient for treatment. However, of the two cases in which electrocoagulation was used<sup>35,36</sup>, one required a new session in a two-year-old patient, even though it was associated with excision in the first approach<sup>36</sup>. This same study reported the need to use dual local anesthesia, topical and subcutaneous lidocaine.

Excision was also used in two case reports through excisional biopsy<sup>37,38</sup>. Usually, the lesions are excised tangentially and have their base cauterized<sup>47</sup>. In one case where the lesions were large, a circumferential incision was performed around each peduncle until the condyloma was completely excised, after which its base was also cauterized<sup>39</sup>. The procedure is related to higher rates of pain, dyspareunia, scar formation, and infection<sup>47</sup>, which, however, was not observed in the studies of the present review.

## CONCLUSION

It is concluded that there are several treatment options for Condyloma Acuminatum for children and adolescents. Imiquimod was the therapy of choice by most authors with high-resolution rates as well as few adverse effects. There is a need for randomized studies and clinical trials, with robust methodologies to reliably point out which therapy is the most effective.

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### **Authors' contribution**

All authors contributed substantially to the study design or data interpretation, participated in draft writing and final version review and approval, and agreed to be responsible for the accuracy or integrity of any part of the study.

### **In the process of creating the review, the following were carried out:**

Data collection and identification: **D, B, S, F, N**

Evaluation of inclusion and exclusion criteria: **D, B, S, F, N**

Data extraction and analysis: **D, B, S, F, N**

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