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## Colorectal Conditions

# Timing of the definitive procedure and ileostomy closure for total colonic aganglionosis HD: Systematic review



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### ABSTRACT

**Aim:** To establish the cogency of recommendations for the appropriate age for pull-through and ileostomy closure in Total Colonic Aganglionosis-Hirschsprung Disease's (TCA-HD).

**Method:** Medline, PubMed, Cochrane, and the ClinicalKey databases were searched without date restriction. The studies that reported TCA-HD cases were evaluated for the number of cases, age at the definitive procedure, age at the ileostomy closure, reported complications, and the type of procedure. Perianal excoriation and diaper rash rates were analyzed using SPSS software, with  $p < 0.05$  considered significant.

**Results:** Twenty-five studies mentioned TCA-HD findings between 1968 and 2019. The total number of patients who had definitive surgery was 218. Analysis showed no correlation between development of diaper rash and the age of the patient at the time of the definitive surgery or ileostomy closure. Studies scored between six and nine of nine possible stars on the NOS scoring system.

**Conclusion:** There is no correlation between age of surgery and postoperative diaper rash. Delaying the definitive procedure or ileostomy closure for TCA-HD has limited support on a review of current studies. The perianal excoriation/diaper rash is not reported in the literature at a high enough frequency to warrant keeping a diverting ileostomy until toilet trained of urine.

**Type of study:** Systematic review and meta-analysis.

Levels of evidence IV

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### Contents

1. Methods . . . . .	2367
1.1. Search strategy . . . . .	2367
1.2. Definitions . . . . .	2367
1.3. Inclusion and exclusion criteria. . . . .	2367
1.4. Quality of included studies. . . . .	2367
1.5. Statistical analysis. . . . .	2368
2. Results . . . . .	2368
3. Discussion . . . . .	2369
References . . . . .	2370

Total Colonic Aganglionosis Hirschsprung's Disease (TCA-HD) forms a small portion of HD; however, the associated morbidity can be devastating to patients and their families [1]. The current approach to manage

a newborn with TCA-HD is obtaining a rectal biopsy to establish the diagnosis and then through laparoscopy or laparotomy determining the extent of aganglionosis by taking biopsies at different levels of the colon and small intestine if needed [2]. Frozen section biopsies are used to determine the positive sites for ganglion cells to create an enterostomy [2]. In the case of TCA-HD, the entire colon does not contain ganglion cells and an ileostomy is created at the first segment of ileum, which contains proper ganglion cells and no hypertrophic nerves, where the point of the leveling procedure is to establish the proper level

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before performing a definitive procedure which is very difficult to revise if the level is wrong [1]. The main advantage of this approach is to obtain a definitive final pathology on the previously taken biopsies before proceeding with a major surgery, which aims at excising the entire colon and completing an ileoanal anastomosis [1,3]. The timing of proctocolectomy and ileoanal anastomosis is still a point of controversy. Performing the pull-through at the early age can be technically difficult and having an ileostomy for a long period can be a challenge because of the associated complications such as electrolyte disturbances, stoma prolapse, stoma stricture, or peristomal skin excoriation [4]. On the other hand, early ileostomy closure may lead to severe perianal excoriation, which can cause significant suffering to the patient and family, and be so devastating that it requires a diverting ileostomy [1]. It also noted a high rate of enterocolitis with early operation/closure and recommended waiting until the child willingly accepts rectal irrigations [5]. These observations led to recommendations to delaying the ileostomy closure and/or definitive procedure.

In 2011, Dr. Peña and Dr. Levitt published their experience with TCA-HD [1]. Their main recommendation was to perform a “colectomy with straight ileoanal anastomosis and ileostomy at presentation”, putting special emphasis on a meticulous technique aimed at preserving an intact anal canal, with focus on not obliterating the dentate line [1]. Ileostomy closure is performed at a later date, only when the child is toilet trained for urine and is willing to tolerate rectal irrigations [1]. The main rationale behind this advice is to avert devastating diaper rash and enterocolitis [1]. These recommendations have become a standard approach, likely because they are more conservative and the perianal excoriation and enterocolitis can be severe. However, a number of studies have revealed different conclusions [6,7]. We hypothesize that there is not enough evidence to support the previously recommended practice [1] of deferring the definitive procedure and/or ileostomy closure until the age of toilet training. The aim of this analytic review is to examine the evidence from the available studies in order to reach a recommendation based on the literature.

## 1. Methods

A Medline, PubMed, Cochrane, and the ClinicalKey databases search was conducted to find studies addressing TCA-HD that mentioned individual or institutional experiences in terms of type of surgery, timing of definitive procedure, timing of ileostomy closure, and any postoperative complication between 1968 and 2019. Particular attention was given to the incidence of diarrhea, incontinence, diaper rash, and perianal excoriation. Excoriation is usually an advanced stage of diaper rash, though these two terms have been used interchangeably in the literature. In order to examine the outcomes first-hand, only case-series, single surgeon, or single institution papers were included. If the patient died before finishing all procedures, their data were excluded. The study by Peña, et al. [1] was used for comparison, but because it included multiple patients with primary interventions by other surgeons and institutions, it was not included in the analysis.

### 1.1. Search strategy

With no date restrictions, the following databases were searched: PubMed, Google Scholar, MEDLINE, Cochrane, and the ClinicalKey in May 2019. The studies included in this review were also searched for any pertinent articles. The literature was explored first by reviewing the abstracts for the information of interest. Only TCA-HD individual/institutional studies were encompassed in this analysis (Fig. 1, Table 1).

### 1.2. Definitions

Throughout this review, the following terms/abbreviations were used:

A. TCA-HD: Total colonic aganglionosis Hirschsprung disease, which can be limited to the colon or include the entire gastrointestinal tract.

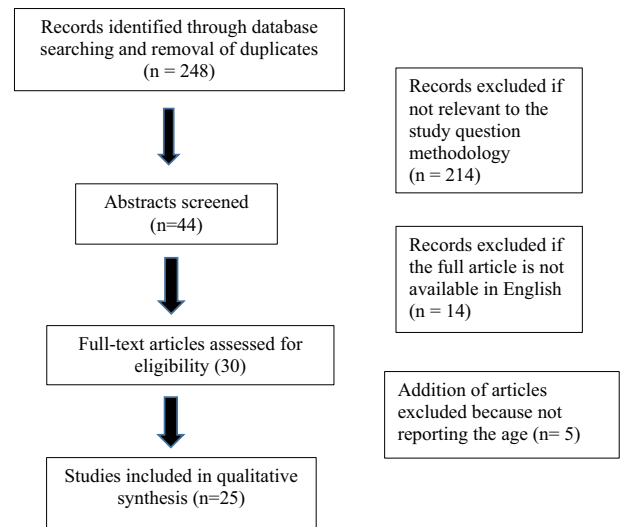


Fig. 1. Flow diagram of study selection.

B. Pull-through: The definitive surgery for TCA-HD involves connecting the ganglionated part of the bowel with the anus. There are many technical approaches used to achieve this goal, including but not limited to: Martin, Duhamel, Soave, Swenson, Modified-Martin, ileal pouch anal anastomoses (IPAA or J pouch) and transanal endorectal pull-through.

### 1.3. Inclusion and exclusion criteria

According to ‘PICOS’ format, inclusion criteria for this review are as follows:

- Population: All children born alive with the diagnosis of TCA-HD who underwent pull-through at any point during their management.
- Intervention: Pull-through procedure irrespective of the portion of bowel used to create the enteroanal anastomosis.
- Control: Children who had pull-through at an early age irrespective of the type of the procedure.
- Outcomes: The main outcome was the incidence of perianal excoriation/diaper rash. Secondary outcomes included the development of incontinence or soiling.
- Study type: Only individual/institutional studies that included newborns with TCA-HD were incorporated in this review; review studies that included HD-TCA patients were used only to relate to the findings of this review.

Two investigators examined the quality of the utilized studies independently; the following exclusion criteria were applied: any study that did not include HD-TCA patients, basic science or animal reports, and comparative studies. Extracted abstracts were scrutinized and further exclusions were applied to all nonrelevant studies and to all the reports that did not mention either the outcomes of interest. Manuscript studies that were considered pertinent by either reviewer were obtained for detailed analysis. A consensus of included studies was reached via thorough discussion under the direction of the senior author.

### 1.4. Quality of included studies

The quality of incorporated studies was examined by two reviewers independently. The Newcastle Ottawa Scale (NOS) was used to evaluate study quality on three broad levels: selection (4 elements), comparability (2 elements), and outcome (3 elements). Each fulfilled quality element was given a star; each study can obtain as many as nine stars (Table 2).

**Table 1**  
The characteristics of included studies.

Study number	First author	Year	Number of patients	Perianal excoriation/diaper rash (percentage)	Diarrhea/soiling/incontinence
1	Martin	1968	5	Yes (20%)	Yes
2	Martin	1972	9	No	Yes
3	Burrington	1976	6	No	No
4	Kimura	1981	3	No	No
5	Martin	1982	4	Yes (100%)	Yes
6	Shandling	1984	2	No	No
7	C. N-Fekete	1986	27	No	Yes
8	Bergmeijer	1988	6	No	Yes
9	Applebaum	1988	2	Yes (100%)	No
10	Kimura	1988	6	No	Yes
11	Shermeta	1989	5	No	Yes
12	Menardi	1989	5	No	No
13	Endo	1994	9	No	Yes
14	Yamagiwa	1995	1	Yes (100%)	Yes
15	Hengster	1996	5	No	No
16	Emslie	1997	5	No	No
17	Coran	2000	20	No	Yes
18	Bonnard	2001	5	No	No
19	Dodero	2001	24	No	No
20	Rintala	2002	10	No	Yes
21	Wildhaber	2005	20	Yes (20%)	Yes
22	Anupama	2007	25	Yes (77.7%)	Yes
23	Cheung	2009	4	Yes (100%)	Yes
24	Yeh	2014	9	Yes (33%)	Yes
25	Hukkinen	2015	21	Yes (4.76%)	No

### 1.5. Statistical analysis

A meta-analysis was conducted for primary and secondary outcomes using RevMan 5.3 (Copenhagen). The random effect model (Mantel–Haenszel approach) was utilized to create standard forest plots of effect size and error bars, with heterogeneity demonstrated for the analysis. Publication outliers were assessed through the creation of a funnel plot of standard error against the log odds ratio, but a

**Table 2**  
Newcastle Ottawa Scale (NOS) for studies quality evaluation.

SID	First author	Selection			Comparability of groups		Outcome			Total
		1	2	3	4	5	6	7	8	
1	Martin	*	*	*	**				***	8
2	Martin	*	*	*	**				*	6
3	Burrington	*	*	*	**				**	7
4	Kimura	*	*	*	**				**	7
5	Martin	*	*	*	**				***	8
6	Shandling	*	*	*	**				***	8
7	C. N-Fekete	*	*	*	**				*	6
8	Bergmeijer	*	*	*	**				*	6
9	Applebaum	*	*	*	**				*	8
10	Kimura	*	*	*	**				**	7
11	Shermeta	*	*	*	**				*	6
12	Menardi	*	*	*	**				*	6
13	Endo	*	*	*	**				*	6
14	Yamagiwa	*	*	*	**				***	8
15	Hengster	*	*	*	**				*	6
16	Emslie	*	*	*	**				*	6
17	Coran	*	*	*	**				**	7
18	Bonnard	*	*	*	**				***	8
19	Dodero	*	*	*	**				***	8
20	Rintala	*	*	*	**				***	6
21	Wildhaber	*	*	*	**				***	8
22	Anupama	*	*	*	**				***	8
23	Cheung	*	*	*	**				***	8
24	Yeh	*	*	*	**				***	8
25	Hukkinen	*	*	*	**				***	8

**Selection:** 1) Representativeness of the exposed cohort, 2) Selection of the non-exposed cohort, 3) Ascertainment of exposure, 4) Presence outcome of interest at start of study.

**Comparability:** 1) The study controls for age, sex and marital status, 2) Study controls for other factors.

**Outcome:** 1) Assessment of outcome, 2) Was follow-up long enough for outcomes to occur, 3) Adequacy of follow-up of cohorts.

statistical estimation of this plot was not considered.  $P < 0.05$  was the cutoff for statistical significance in all analyses.

## 2. Results

Twenty-five studies were identified as shown in Table 1 [5–29]. The total number of patients found was 218. For these 25 studies, the average age of the patient at the time of the definitive procedure was 12.8 months (1–60 months) and the median was 12.0 months. Regarding the ileostomy closure, 24% studies did not mention it at all (6/25), but the majority performed the closure ileostomy as a part of the definitive surgery (50%, 14/28). Few stated a specific time for closure, which ranged from 1 month to 5 years with a mean of 6 months. It is worth noting that most ileostomy closures are conducted about 6 months after the definitive procedure. In one study, which included four patients, ileostomy had never been created and all the patients developed perineal excoriation which was treated conservatively and resolved within a few months [12].

Regarding the perianal excoriation/diaper rash, 10 studies, with a total of 122 patients, stated that 49 patients (41.2%) developed diaper rash. The rate was anywhere from 0% to 100%; however, the majority did not discuss the severity of the rash, and almost all of the cases resolved with medical management, except for six which had to have an ileostomy (Figs. 3 and 4). Four studies reported a rash 100% of the time, but also mentioned the rash was minor and transient [12,16,21,28]. Only Hukkin's studies specified the degree of rash as severe in 4.8% of their patients [7]. Eleven studies (44%) mentioned postoperative complications but diaper rash/perianal excoriation was not among of them [5,12–21]. Loperamide, thickened food, and prophylactic perineal care were among the measures that helped treat and avoid diaper rash. The average time for diarrhea/incontinence to resolve ranged from several months to a few years. According to the studies that reported the age at the time of surgery and percentage of patients with diaper rash, there was no significant association between the development of perianal excoriation and age of the patient at the definitive procedure ( $P = 0.619$ ) or age of the patient at closure of the ileostomy ( $p = 0.437$ ) (Fig. 2). However, only eight studies have been performed since 2000. Only five reported the age at the time of definitive procedure and ileostomy closure. When the statistical analysis only included these studies, we found a negative correlation between the age at the definitive procedure

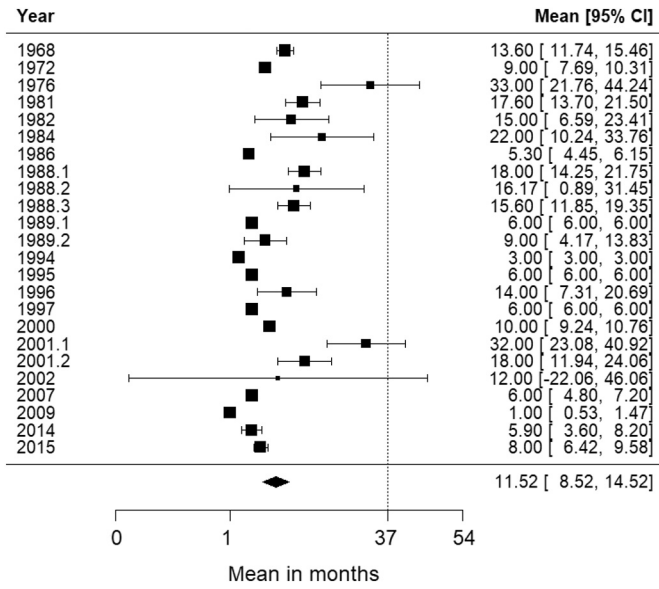


Fig. 2. Forest plot of age at the time of the definitive procedure.

and the development of diaper rash ( $-0.9276337$ ,  $p = 0.007$ ), but there was no correlation between the age at the time of ileostomy closure and the development of diaper rash ( $p = 0.658$ ).

Two studies adopted the recommendations of performing the definitive procedure when toilet trained of urine to avoid devastating perianal excoriation [5,14]. However, the author of the second study stated that, “we have performed endorectal pull-through procedures on 3 newborns and noted defecation frequency similar to those of older children with total colonic Hirschsprung’s disease” [5]. Nonetheless, there was no concordance on the age of toilet training, which ranged from 22 to 54 months with a mean age of 37 months [30].

The study by Peña, et al. presented 27 patients; 12 patients had the primary pull-through performed by Dr. Peña and his team, and 15 were operated on elsewhere [1]. Of these, 10 (66%) developed severe diaper rash, and two of those patients had a “destroyed anal canal” during surgery.

Regarding the rate of perineal excoriation reported chronologically, there was no pattern of less or more over time. The first study, which was published in 1968 using the Martin technique, had a 20% rate of perineal excoriation, while the last published study in 2015 had a rate of 4.76% using the ileoanal anastomosis technique.

An in-depth look at all studies revealed that all the definitive procedures were done prior to the mean age of toilet training (37 months). Only three studies performed the ileostomy closure after the 24 months.

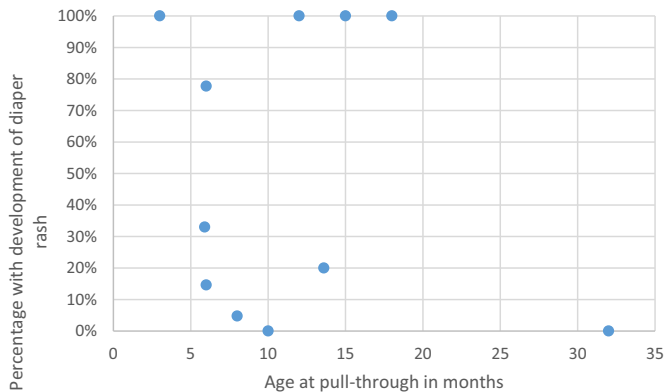


Fig. 3. Relationship between age at pull through and diaper rash.

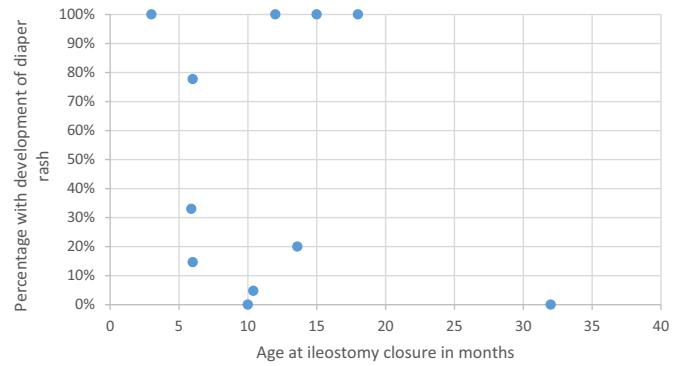


Fig. 4. Relationship between age at ileostomy closure and diaper rash.

Additionally, evolvement of diaper rash ranged from 0% to 100%, but there was no pattern based on the age at the time of the definitive procedure and/or ileostomy closure.

### 3. Discussion

Based on the frequent occurrence of severe perianal excoriation, Dr. Peña’s team recommended initial straight pull-through with diverting ileostomy be performed at birth followed by ileostomy closure when the patient is toilet trained of urine and willing to tolerate irrigations in order to avoid diaper rash and enterocolitis [1]. While we understand the basis of Dr. Peña’s recommendations and the potential devastating consequences of early ileostomy closure, other studies report lower rates of severe perianal excoriation [6,7] [13]. As his study acknowledges, included patients that had a pull-through done elsewhere represent a highly biased group that is not necessarily representative of all patients operated on for total colonic aganglionosis. The higher rates of severe degrees of perianal excoriation among certain transferred patients may be because of selection bias in that cases that develop complications that cannot be treated locally are sent for further management by his team. In that study, 10 patients of 15 operated on elsewhere (66%) developed severe diaper rash [1]. However, two of them had a “destroyed anal canal,” which can occur by starting the dissection/anastomosis at or very close to the dentate line [1], which means the rash was most likely owing to loss of anal sphincter rather than the age at the time of surgery. Hence, the number of patients with a normal anal canal and severe perianal excoriation should be 8 of 13 (61%). This is significantly more than the rate reported in our combined analysis.

The first paper by Coran et al., recommended the same principle of waiting until toilet trained; however, this study also reported that they performed endorectal pull-through procedures on three newborns and the results in terms of defecation frequency were very comparable to older children [5]. Additionally, the paper by Wildhaber et al., (Dr. Coran’s most recent study) reported the entire cohort received the surgery either as neonates or around the age of 1 year, and closure of the ileostomy occurred at the same time of the pull-through for the latter group [13]. In addition, there was no recommendation about delaying the definitive procedure or the closure until the toilet training age, and the reported rate of perineal excoriation was only 20% [13]. Moreover, while the study by Coran, et al. advocated for delaying the definitive procedure until toilet-training age, the surgeries of his cohort were done either on newborns (6) or children at the age of 1 year and none reported any perineal excoriation [5]. In answering questions after presenting a study with a 41 patients, Spitz reported he thought that the best time for the definitive procedure is six months [31]. In of their cohort, six patients (14.6%) developed severe perineal excoriation or intractable stool incontinence and underwent permanent ileostomy [31].

Another issue that could affect the outcomes of these studies is anal sphincter destruction that was only reported by the study by Peña, et al. With anal sphincter destruction (injury to sphincter muscle, or loss of



dentate line) soiling will develop and perianal excoriation will evolve consequently regardless of ileostomy closure age. Therefore, it could be the reason behind diaper rash in some other studies.

A systematic review study reported that overall TCA-HD's postoperative complications, including perianal excoriation (although not individually analyzed), were not associated with the type of surgery based on, and perianal excoriation was reported only in 2 of 19 included studies within the mean follow up period (3.9 years), and the majority of children were continent [3]. The same study recommends that the type of the definitive procedure should be surgeon and center based [3]. Because that has been published in a previous systematic review, we did not include the type of surgery in this paper [3]. In the absence of a clearly superior choice, we recommend clinicians choose the time for the definitive procedure and ileostomy closure based on their personal experience and comfort, as well as counseling the child's caregiver regarding the advantages and drawbacks of each option.

The limitations to our review are that the extent and the medical management of diaper rash are not well documented in all of the studies.

Furthermore there was no consensus is toilet-training age, the three studies that used this term had a range from 22 to 48 months [5,10,14]. The main flaw of this study is the failure to reveal the most appropriate age for the main procedure and ileostomy closure owing to the lack of precise reporting that correlates the age of definitive surgery with the development of perineal excoriation. Another limitation is the deficiency of data regarding quality of life and analysis of the direct cost of the long wait until ostomy reversal and its related expenses versus a short wait and its potential consequences for perineal excoriation and difficult medical management. The practical value of this review relies on the quality of the analyzed studies included within it; in the absence of any RCT and the wide range of differences in reporting diaper rash rates across all explored studies, firm conclusions cannot be reached with the available data. Thus, an analysis of the current literature does not point to an optimum age for primary pull through and ileostomy takedown.

It is worth noting that this study included all the published studies concerning this topic from more than half a century (1968–2018). Time-based and geographic variations in practices may explain some differences in the outcomes over time. Also, it may have weakened our conclusions thus preventing us from ascertaining the best practice, and relatively high statistical heterogeneity between studies supports this probability. The main advantage of this study is that it analyzed all accessible data concerning this topic from more than half a century (1968–2018), and shed light on the strength of the current guidelines.

Future RCT research on a multi-institutional level should be conducted with detailed documentation of preoperative comorbidities, intraoperative complications, timing of definitive procedures, and postoperative courses with measurement of the quality of life of the patients and their families and the economic burden of each approach. Such a study can determine the most appropriate time for the definitive procedure for HD-TCA and ileostomy closure and avoid the potential downsides of the reported approaches.

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