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Time-dependent management of Hirschsprung disease during Covid-19 pandemic --Manuscript Draft--

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Abstract:	<p>INTRODUCTION</p> <p>During Covid-19 pandemic, some elective non-deferrable surgical procedures has been maintained on a local basis to avoid complications of time-dependent issues. The aim of this paper is to suggest a possible strategy for the management of patients with Hirschsprung (HSCR) during this dramatic Covid-19 pandemic considering.</p> <p>MATERIALS AND METHODS</p> <p>A systematic literature search on PubMed and Embase of all available literature addressing "Hirschsprung", "preoperative enterocolitis", "preoperative mortality", "complications", and "timing" in all possible combination has been performed limiting documents to the last 10 years and excluding non-English papers.</p> <p>RESULTS</p> <p>Systematic review assessed 170 papers and focused on 10 full-text papers addressing the same issues as above. The incidence of preoperative HAEC proved to be as high as 34% with a mortality between 2.4% and 8%. Age at surgery varied in literature reports but recent evidences suggested that patients should be operated around 3 months of age after effective bowel decompression. Rectal irrigations should not be continued over 2 to 4 months to avoid nutritional issues and subsequent possible increase of surgical complications.</p> <p>CONCLUSIONS</p> <p>Based on available literature, contingent shortage of health resources and necessity to</p>

avoid hospital overcrowding during this pandemic, we suggest as follows: 1) surgery should be delayed for healthy neonates up to 3 months of age, and a diverting enterostomy consider for those with ultralong HSCR, unwell or with ineffective nursing; 2) surgery can be delayed but rectal irrigations cannot be maintained indefinitely (ideally within 2 to 4 months at maximum); 3) Surgery could be postponed in older patients, provided previous bouts of HAEC are excluded. This chosen behaviour of our Center for Digestive Diseases aims at avoiding risk of complication and serve the best for our patients in this delicate setting of Covid-19 pandemic.

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Time-dependent management of Hirschsprung disease during Covid-19 pandemic

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ABSTRACT

INTRODUCTION – During Covid-19 pandemic, some elective non-deferrable surgical procedures has been maintained on a local basis to avoid complications of time-dependent issues. The aim of this paper is to suggest a possible strategy for the management of patients with Hirschsprung (HSCR) during this dramatic Covid-19 pandemic considering.

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RESULTS – Systematic review assessed 170 papers and focused on 10 full-text papers addressing the same issues as above. The incidence of preoperative HAEC proved to be as high as 34% with a mortality between 2.4% and 8%. Age at surgery varied in literature reports but recent evidences suggested that patients should be operated around 3 months of age after effective bowel decompression. Rectal irrigations should not be continued over 2 to 4 months to avoid nutritional issues and subsequent possible increase of surgical complications.

CONCLUSIONS – Based on available literature, contingent shortage of health resources and necessity to avoid hospital overcrowding during this pandemic, we suggest as follows: 1) surgery should be delayed for healthy neonates up to 3 months of age, and a diverting enterostomy consider for those with ultralong HSCR, unwell or with ineffective nursing; 2) surgery can be delayed but rectal irrigations cannot be maintained indefinitely (ideally within 2 to 4 months at maximum); 3) Surgery could be postponed in older patients, provided previous bouts of HAEC are excluded. This chosen behaviour of our Center for Digestive Diseases aims at avoiding risk of complication and serve the best for our patients in this delicate setting of Covid-19 pandemic.

INTRODUCTION

Since late February, when Covid-19 outbreak reached Europe, Italy in particular, a number of countermeasures have been introduced in order to reduce people flows throughout countries and decrease the likelihood of infection diffusion. Since the 7th of March 2020 Italy (and other countries during the following weeks) mandated social distancing and redistributed Public and Private Health Resources. All Hospitals have been involved in treatment of Covid-19 patients of all ages. In areas where virus outbreak proved to be particularly severe, most Hospitals have been converted into Covid-Hospitals and most resources have been dedicated to this dramatic issue. The aim of these countermeasures is to contain the outbreak (avoid useless people movements) and to cope with the peak of incidence of Covid-19-positive cases.

In this dramatic scenario children keep injuring themselves, falling sick and having severe diseases requiring surgery. Of note, we must underline that they proved to be less susceptible to Covid-19 both in terms of incidence and severity of the infection [1-3].

On the ground of these considerations, most European countries cancelled all elective deferrable surgeries. Urgencies and emergencies have been ensured and a selection of elective non-deferrable surgical procedures have been maintained on a local basis to avoid complications of time-dependent issues (in terms of survival and functional results).

Hirschsprung's disease (HSCR) is a rare congenital anomaly of the enteric nervous system that represents the most frequent cause of neonatal intestinal obstruction. The disease occurs in 1 into 5000 live births and can be complicated by up to 60% enterocolitis (HAEC) with up to 10 % mortality, which mostly occur preoperatively, in the neonatal period and in syndromic patients [4]. The risk of preoperative HAEC occurrences with their morbidity and mortality as well as the risk-benefit ratio of delaying surgery during this Covid-19 pandemic represent the focus of this paper aimed at suggesting a possible strategy for the management of patients with HSCR in this delicate scenario.

METHODOLOGY

Systematic Review

The Author performed an extensive PubMed and Embase research with the terms “Hirschsprung”, “preoperative enterocolitis”, “preoperative mortality”, “complications”, and “timing” in all possible combination in order to address all issues that can be involved in a decision-making process for HSCR management. Papers older than 10 years and non-English literature was excluded.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

This methodology was used to report significant and homogeneous results of the systematic review.

Definitions

- *Classic-HSCR* is defined as aganglionosis limited to the splenic flexure
- *Long-HSCR* is defined as aganglionosis extending up to the right colon
- *Ultralong-HSCR* is defined as aganglionosis involving the whole colon and extending up to the terminal ileum

Statistical analysis

Statistical analysis was used to address the salient data extracted from the personal series of HSCR patients seen by the Authors. Descriptive statistics were reported as absolute frequencies and percentages. Median and ranges were used to describe semi quantitative and quantitative variables. Two tailed Fisher’s exact test was used to compare categorical variables. Unpaired t test was used to compare continuous variables. A p lower than 0.05 was considered to be statistically significant.

RESULTS

PRISMA

One-hundred and seventy papers were identified through PubMed and Embase searches. After duplicate removal and screening for language and adherence to the topic, a total of 26 papers were screened for relevance. A total of 15 full-text papers were assessed for eligibility. Five documents were excluded as dealing with post-mortem only or as wrongly focused. A total of 10 full-text papers turned out to be eligible to address all concerns related to timing for surgery in patients with HSCR [5-14]. See Figure 1 for PRISMA details and Table 2 for the list of selected full-text papers.

Preoperative HAEC, morbidity and mortality

This is the most frequent, severe and potentially fatal preoperative complication of HSCR patients, which can be devastating particularly in newborns or in patients with congenital heart diseases [4]. The selected papers suggested a weighted median incidence of 12% (ranging between 8% to 34%) [8-10,12-14]. Although preoperative HAEC mortality decreased over time [13], it is still reported and occurs with a median incidence of 6% (ranging between 2.4% and 8% [10,13]) thus posing an important burden on the treatment of the disease. Some Authors suggested that older age at diagnosis [7], low birth weight, and extended aganglionosis [9,12] could represent predisposing factors for preoperative HAEC occurrences. Preoperative HAEC seem to have significant morbidity, as they can increase early readmission and impact on short-term outcome [5]. Moreover, preoperative HAEC increases HAEC predisposition in the postoperative period [10] and impairs overall functional outcome in terms of continence [14].

Age at surgery and time-span between diagnosis and surgery

There is no consensus amongst pediatric surgeons on when to operate a patient with HSCR. During the last decades we observed a progressive reduction of the age at surgery. Cass in 1986 suggested that the earlier is the better [15], Jiang ZX and co-workers in 1994 suggested surgery to be done in the neonatal period [16]. On the other hand, recent evidences suggested that newborns can safely wait a couple of months before being operated as most reports suggest that surgery should be performed between 2 and 4 months of age [6,7,9-12]. Only a minority of surgeons operate at an older age [5,13]. As a matter of facts, we basically ignore the average timespan between diagnosis

and surgery as it is never reported in these papers. Noteworthy, a UK survey by Huddard in 1998 suggested that 73% of surgeons would operate on HSCR within a month since diagnosis [17]. Only two papers in our systematic review addressed this issue and suggested to wait an average of 9 weeks (ranging between 6 weeks and 2 to 4 months) when a neonate receive a diagnosis of HSCR [7,9]. Even so we do not know what most surgeons would do in case of delayed diagnoses (those occurring outside neonatal period) as none reported nor indicated the expected delay between diagnosis and surgery in various age groups.

DISCUSSION

During Covid-19 pandemic, pediatric surgeons have to determine which surgical procedures can be delayed avoiding hospital overcrowding and optimize the use of health resources, always maintaining the highest safety for the patients. The first issue is “*how long should we postpone surgery?*”. Different countries reacted differently to this pandemic, mostly without posing a definite deadline on these limitations. On the other hand, UK national health system proposed 3 months starting since the 15th of April as a reliable period of time for the suspension of all elective surgical procedures [18]. This deadline seems reasonable and could be considered to determine whether pediatric patients with rare diseases can pass safely through this delay. In this scenario, the question “*can radical surgery for HSCR be delayed or not?*” ... is a tough one that needs an integrated answer for such a rare and potentially severe congenital malformation. When addressing timing for surgery in a patient with HSCR a crucial aspect that needs to be considered is represented by the risk of developing preoperative complications (HAEC above all) with their subsequent morbidity and mortality. This issue must be balanced against the side effects of surgery in various age groups and those of limitations posed by present pandemic criticalities.

HAEC, experienced by 25% to 35% of patients, can represent the presenting symptom in 25% of infants with HSCR [19]. Those are the patients carrying the highest mortality [4,19,20,21]. We recently demonstrated that neonates and infants with HSCR, particularly those with associated major congenital heart diseases, are those carrying the highest mortality, which occurs mostly in the preoperative period [4]. Of note, a particular subset of HSCR, those with Down Syndrome (DS) seem to have a higher risk of developing severe HAEC [14,22]. A reason for the susceptibility and fragility of these patients is likely related to the well-known abnormalities of their immune system and to the high prevalence of associated major congenital heart defects [23].

HAEC can also determine important effects in the long-term. A paper by Menezes and Puri in 2006 demonstrated that patients who developed preoperative HAEC present a significantly higher incidence of postoperative continence issues (22% vs 55% $p = 0.0001$). Accordingly, a more recent paper from Lee and coworkers showed that preoperative HAEC do correlate with a higher likelihood of postoperative complications [14]. Furthermore, as confirmed by Huang in 2017 [12], Pruitt in 2019 [10], as well as by

our group in 2008 [24], preoperative HAEC occurrences predispose to postoperative HAEC recurrences that significantly increase the need for hospitalization and important health resources requirements, as recently confirmed by Quiroz [5].

Available literature data failed in clarifying the ideal timing from diagnosis to surgery, as confirmed by the systematic review that we performed to address this issue. Most pediatric surgeons focused on age at surgery but not on the timespan from diagnosis. The 90's were years of innovation and enthusiasm. This was the era of neonatal surgery and precocious treatment of HSCR [15,16,25,26]. Huddard in 1998 [17] in his UK nationwide survey confirmed that the vast majority of surgeons in UK would operate their babies within a month since diagnosis. Things changed during the last decades and a recent EUPSA survey by Zani and colleagues in 2017 reported that only one third of surgeons would operate HSCR in the very neonatal period, whereas two thirds would wait longer (usually after 4 months and 5 kilograms weight) [27]. This is a sort of countertendency of pediatric surgeons that are moving from early neonatal to delayed infant surgery. This attitude is confirmed by many Authors worldwide, who suggest moving radical treatment to around 3 months of age in order to achieve the best results [6,7,9-12]. Even so, the biggest BIAS of reviewed literature is represented by the predominant inclusion of neonates with a diagnosis performed before one month of age, which is increasing in recent years. Nonetheless, the disease is not unfrequently missed in the neonatal period and can be diagnosed later or, even in adolescents and adults. This aspect is crucial in order to determine the real priority for surgery in patients carrying this rare disease. Of note, some Authors reported that age at surgery does not correlate with a higher incidence of complications [6,24] and this is presumably due to the fact that older diagnoses are reached in patients with less severe forms of the disease, at least from an HAEC point of view.

To summarize, the incidence of potentially fatal preoperative HAEC complicating the whole picture of an HSCR patient represents the reason why to proceed straight to radical treatment. Nonetheless, a reasonable surgical delay could improve long-term outcome, reduce hospitalization and simplify surgical treatment. If we want to guide pediatric surgeons during this Covid-19 pandemic in order to decide when to schedule an HSCR patient for radical pull-through, we need to consider all these issues in the context of redistributed health resources and readdressed priorities.

Noteworthy, the sole unchanged priority should be the well-being of our children and the need to provide the best treatment available, even in this delicate scenario. On the ground of all these considerations, provided hospital facilities can safely assist HSCR patients undergoing major gastrointestinal surgery, we can list a number of key-point to define timing for a pull-through during this pandemic and, probably, during the next 12 months or even longer. The decision-making process for defining the priority should be that of considering each HSCR patients separately with personalized prioritization, based on HAEC risk factors, patient's fragility and concomitant social environment (Figure 2).

Most Authors would agree that a patient with HSCR requires urgent surgery in case a levelling enterostomy is needed. This occurs in ultralong forms, lack of improvement with rectal irrigation (for bowel decompression), and in case of acute and unresponsive HAEC that represent a minority of the whole HSCR population [6,7,9-12,15-17,25-27].

Most HSCR patients can safely tolerate a period of rectal irrigations to reach an adequate age and undergo a safe pull-through with a reasonably low risk of preoperative HAEC [6,7,9-12,27]. Nonetheless, rectal irrigations cannot be performed indefinitely (as recently demonstrated by Lu and co-workers who suggested not to exceed 2-4 months of rectal irrigations to avoid deterioration of nutritional status [7]). On the ground of these considerations, based on the likely suspension of all elective non-urgent procedures during this Covid-19 pandemic for the next 3 months (presumably up to mid-summer) [18], our Center for Digestive Diseases developed the following algorithm to determine the timing for radical treatment of patients with HSCR:

- All neonates and infants with ultralong HSCR should receive a levelling enterostomy as a non-deferrable procedure and reconstructive surgery be postponed to the end of this Covid-19 pandemic or when feasible and convenient according to local guidelines on for outbreak control.
- All neonates with classic to long HSCR should receive prompt bowel decompression and rectal irrigations with bowel nursing.
 - In case of effective nursing and adequate parental background, a full-term, otherwise healthy, HSCR neonate should undergo pull-through after the 3rd month of age in order to achieve a safe pull-through with a reasonably low likelihood of surgical complications [6,7,9-11,13].

- In case of risk factors, such as severe congenital heart malformations, low birth-weight, impossible or inadequate nursing, unreliable parental and/or familial background, and high HAEC scores according to Pastor criteria [7,28], the neonate with HSCR should undergo levelling enterostomy and undergo a safer pull-through at the end of this pandemic.
- All patients carrying a well-functioning enterostomy, regardless of the extent of aganglionosis should wait till the end of this pandemic before undergoing radical surgery.
- Infants already diagnosed with HSCR, waiting for radical surgery who are receiving effective regular rectal irrigations for bowel decompression could be postponed but should not wait longer than overall 3 to 4 months since the beginning of colonic nursing in order to avoid the likely increase of cumulative risk of HAEC threatening survival [4,19] and to reduce the risk of malnutrition with its obvious consequences in terms of possible postoperative complications [7].
- Children and adolescent with a delayed diagnosis should be considered with personalized treatment according to their specific risk factors. Provided those patients did not experienced HAEC before diagnosis (increasing the risk of subsequent HAEC), they could be scheduled with a lower priority, and rectal irrigations that can be carried out even longer than 3 to 4 months.

Regardless of surgery, all families of patients with HSCR should be well educated regarding the risk of HAEC and how to suspect and treat it by bowel decompression. The opportunity to perform a levelling enterostomy should be always weighed against that of a protected nursing basing on the socio-economic parental situation and the possibility to assess the patient on a regular basis. Hospitals should implement protection strategies (dedicated mobile phones, call-centers, etc) in order to be able to assist patients with suspected HAEC occurring either preoperatively or postoperatively. In fact, given the complex scenario of Covid-19 pandemic, we're observing under-referral and underdiagnosis of potentially fatal complications related to the well-known virus phobia related to hospital settings. Although we believe that we will go back to conventional behaviour once this Covid-19 pandemic will be over, some more evidences on the best timing from diagnosis to surgery will be useful to assist pediatric surgeons to deliver the best treatment and serve the best for their patients.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: All Authors declare that they have no potential conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

REFERENCES

1. Brodin P. Why is COVID-19 so mild in children? *Acta Paediatr.* 2020 Mar 2 DOI: 10.1111/apa.15271 PMID: 32212348
2. Caselli D, Aricò M. 2019-nCoV: Polite with children! *Pediatr Rep.* 2020 Feb 11;12(1):8495. doi: 10.4081/pr.2020.8495. eCollection 2020 Feb 11. PMID: 32153742
3. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? *J Microbiol Immunol Infect.* 2020 Feb 25. pii: S1684-1182(20)30039-6. doi: 10.1016/j.jmii.2020.02.011. [Epub ahead of print] PMID: 32147409
4. Pini Prato A, Rossi V, Avanzini S, Mattioli G, Disma N, Jasonni V. Hirschsprung's disease: what about mortality? *Pediatr Surg Int.* 2011 May;27(5):473-8. doi: 10.1007/s00383-010-2848-2. Review. PubMed PMID: 21253751.
5. Quiroz HJ, Perez EA, Franklin KN, Willobee BA, Ferrantella AR, Parreco JP, Lasko DS, Thorson CM, Sola JE. Pull-through procedure in children with Hirschsprung disease: A nationwide analysis on postoperative outcomes. *J Pediatr Surg.* 2020 Jan 31. pii: S0022-3468(20)30077-4. doi: 10.1016/j.jpedsurg.2020.01.038. [Epub ahead of print] PubMed PMID: 32063369.
6. Zhu T, Sun X, Wei M, Yi B, Zhao X, Wang W, Feng J. Optimal time for single-stage pull-through colectomy in infants with short-segment Hirschsprung disease. *Int J Colorectal Dis.* 2019 Feb;34(2):255-259. doi: 10.1007/s00384-018-3179-3. Epub 2018 Oct 27. PubMed PMID: 30368570.
7. Lu C, Xie H, Li H, Geng Q, Chen H, Mo X, Tang W. Feasibility and efficacy of home rectal irrigation in neonates and early infancy with Hirschsprung disease. *Pediatr Surg Int.* 2019 Nov;35(11):1245-1253. doi: 10.1007/s00383-019-04552-8. Epub 2019 Sep 18. PubMed PMID: 31535199.
8. Yulianda D, Sati AI, Makhmudi A, Gunadi. Risk factors of preoperative Hirschsprung-associated enterocolitis. *BMC Proc.* 2019 Dec 16;13(Suppl 11):18. doi: 10.1186/s12919-019-0172-y. eCollection 2019. PubMed PMID: 31890011; PubMed Central PMCID: PMC6912936.
9. Le-Nguyen A, Righini-Grunder F, Piché N, Faure C, Aspirot A. Factors influencing the incidence of Hirschsprung associated enterocolitis (HAEC). *J Pediatr Surg.* 2019 May;54(5):959-963. doi: 10.1016/j.jpedsurg.2019.01.026. Epub 2019 Jan 31. PubMed PMID: 30808539.

10. Pruitt LCC, Skarda DE, Rollins MD, Bucher BT. Hirschsprung-associated enterocolitis in children treated at US children's hospitals. *J Pediatr Surg.* 2020 Mar;55(3):535-540. doi: 10.1016/j.jpedsurg.2019.10.060. Epub 2019 Nov 20. PubMed PMID: 31836243.
11. Freedman-Weiss MR, Chiu AS, Caty MG, Solomon DG. Delay in operation for Hirschsprung Disease is associated with decreased length of stay: a 5-Year NSQIP-Peds analysis. *J Perinatol.* 2019 Aug;39(8):1105-1110. doi: 10.1038/s41372-019-0405-y. Epub 2019 Jun 17. PubMed PMID: 31209278.
12. Huang WK, Li XL, Zhang J, Zhang SC. Prevalence, Risk Factors, and Prognosis of Postoperative Complications after Surgery for Hirschsprung Disease. *J Gastrointest Surg.* 2018 Feb;22(2):335-343. doi: 10.1007/s11605-017-3596-6. Epub 2017 Sep 27. PubMed PMID: 28956279.
13. Taguchi T, Obata S, Ieiri S. Current status of Hirschsprung's disease: based on a nationwide survey of Japan. *Pediatr Surg Int.* 2017 Apr;33(4):497-504. doi: 10.1007/s00383-016-4054-3. Epub 2017 Jan 5. PubMed PMID: 28058486.
14. Lee CC, Lien R, Chiang MC, Yang PH, Chu SM, Fu JH, Lai JY. Clinical impacts of delayed diagnosis of Hirschsprung's disease in newborn infants. *Pediatr Neonatol.* 2012 Apr;53(2):133-7. doi: 10.1016/j.pedneo.2012.01.011. Epub 2012 Mar 7. Erratum in: *Pediatr Neonatol.* 2012 Jun;53(3):216. Chian, Ming-Chou [corrected to Chiang, Ming-Chou]. PubMed PMID: 22503261.
15. Cass D. Hirschsprung's disease: an historical review. *Prog Pediatr Surg.* 1986;20:199-214. PubMed PMID: 3095874.
16. Jiang ZX, Hu JG, Lu JS. [Timing of radical operation on Hirschsprung's disease in newborns]. *Zhonghua Wai Ke Za Zhi.* 1994 Dec;32(12):715-7. Chinese. PubMe PMID: 7774416.
17. Huddart SN. Hirschsprung's disease: present UK practice. *Ann R Coll Surg Engl.* 1998 Jan;80(1):46-8. PubMed PMID: 9579127; PubMed Central PMCID: PMC2502752.
18. Iacobucci G. Covid-19: all non-urgent elective surgery is suspended for at least three months in England. *BMJ.* 2020 Mar 18;368:m1106. doi: 10.1136/bmj.m1106. PubMed PMID: 32188602.
19. Gosain A. Established and emerging concepts in Hirschsprung's-associated enterocolitis. *Pediatr Surg Int.* 2016 Apr;32(4):313-20. doi: 10.1007/s00383-016-3862-9. Epub 2016 Jan 19. Review. PubMed PMID: 26783087; PubMed Central PMCID: PMC5321668.

20. Peres LC, Cohen MC. Sudden unexpected early neonatal death due to undiagnosed Hirschsprung disease enterocolitis: a report of two cases and literature review. *Forensic Sci Med Pathol*. 2013 Dec;9(4):558-63. doi: 10.1007/s12024-013-9465-z. Epub 2013 Jul 11. Review. PubMed PMID: 23842858.
21. Garg SR, Sathe PA, Taware AC, Surve KM. Fatal Toxic Megacolon in a Child of Hirschsprung Disease. *J Clin Diagn Res*. 2016 Dec;10(12):ED03-ED05. doi: 10.7860/JCDR/2016/21075.9083. Epub 2016 Dec 1. PubMed PMID: 28208866; PubMed Central PMCID: PMC5296439.
22. Halleran DR, Ahmad H, Maloof E, Paradiso M, Lehmkuhl H, Minneci PC, Levitt MA, Wood RJ. Does Hirschsprung-Associated Enterocolitis Differ in Children With and Without Down Syndrome? *J Surg Res*. 2020 Jan;245:564-568. doi: 10.1016/j.jss.2019.06.086. Epub 2019 Aug 30. PubMed PMID: 31476645.
23. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. *Clin Exp Immunol*. 2011 Apr;164(1):9-16. doi: 10.1111/j.1365-2249.2011.04335.x. Epub 2011 Feb 24. Review. PubMed PMID: 21352207; PubMed Central PMCID: PMC3074212
24. Pini Prato A, Gentilino V, Giunta C, Avanzini S, Mattioli G, Parodi S, Martucciello G, Jasonni V. Hirschsprung disease: do risk factors of poor surgical outcome exist? *J Pediatr Surg*. 2008 Apr;43(4):612-9. doi: 10.1016/j.jpedsurg.2007.10.007. PubMed PMID: 18405705.
25. Carcassonne M, Guys JM, Morrison-Lacombe G, Kreitmann B. Management of Hirschsprung's disease: curative surgery before 3 months of age. *J Pediatr Surg*. 1989 Oct;24(10):1032-4. Review. PubMed PMID: 2681654.
26. Sarioğlu A, Tanyel FC, Büyükpamukçu N, Hiçsönmez A. Clinical risk factors of Hirschsprung-associated enterocolitis. I: Preoperative enterocolitis. *Turk J Pediatr*. 1997 Jan-Mar;39(1):81-9. PubMed PMID: 10868198.
27. Zani A, Eaton S, Morini F, Puri P, Rintala R, Heurn EV, Lukac M, Bagolan P, Kuebler JF, Friedmacher F, Wijnen R, Tovar JA, Hoellwarth ME, Pierro A; EUPSA Network Office. European Paediatric Surgeons' Association Survey on the Management of Hirschsprung Disease. *Eur J Pediatr Surg*. 2017 Feb;27(1):96-101. doi: 10.1055/s-0036-1593991. Epub 2016 Nov 29. PubMed PMID: 27898990.
28. Pastor AC, Osman F, Teitelbaum DH, Caty MG, Langer JC. Development of a standardized definition for Hirschsprung's-associated enterocolitis: a Delphi analysis. *J Pediatr Surg*. 2009 Jan;44(1):251-6. doi: 10.1016/j.jpedsurg.2008.10.052. PubMed PMID: 19159752.

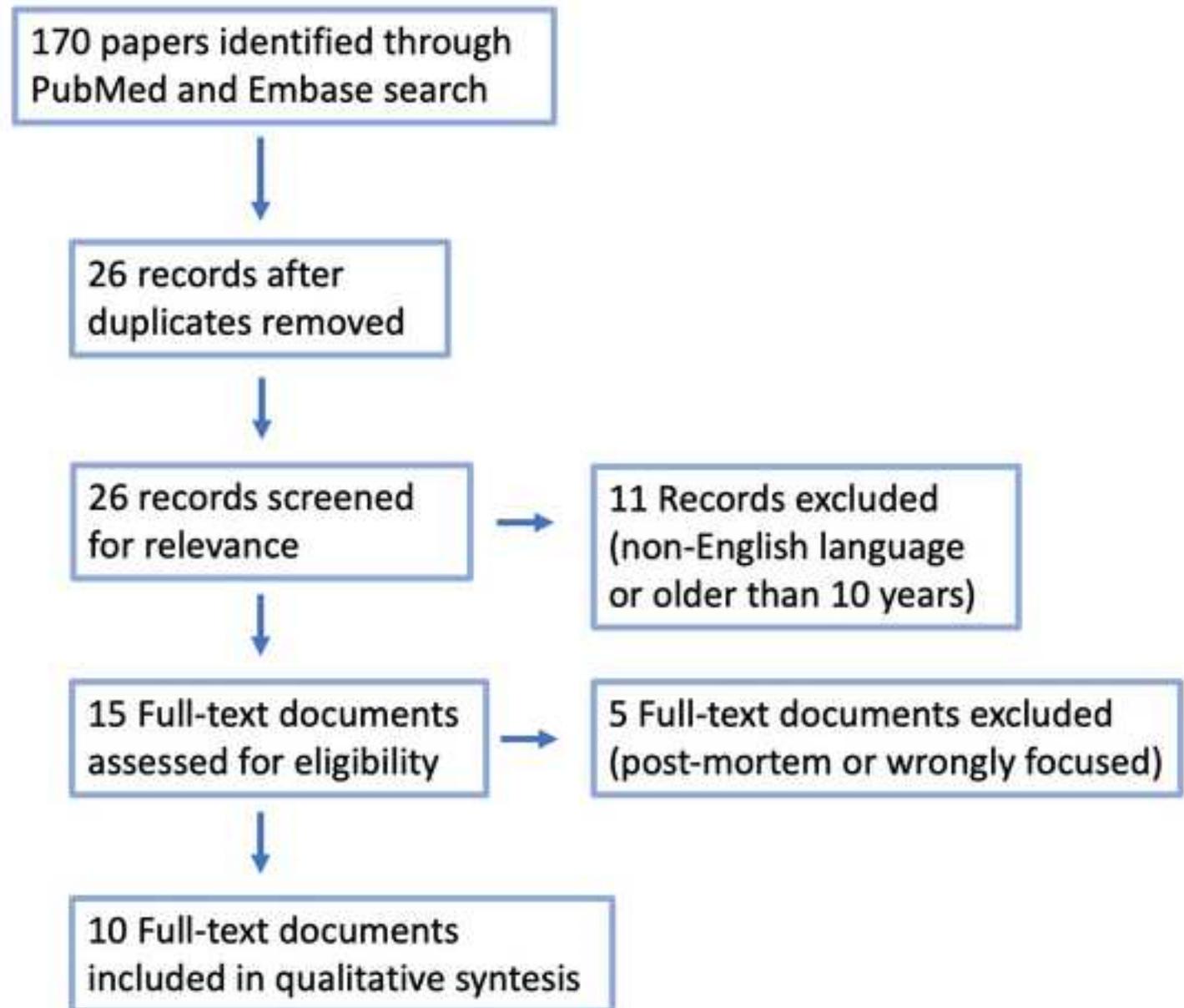
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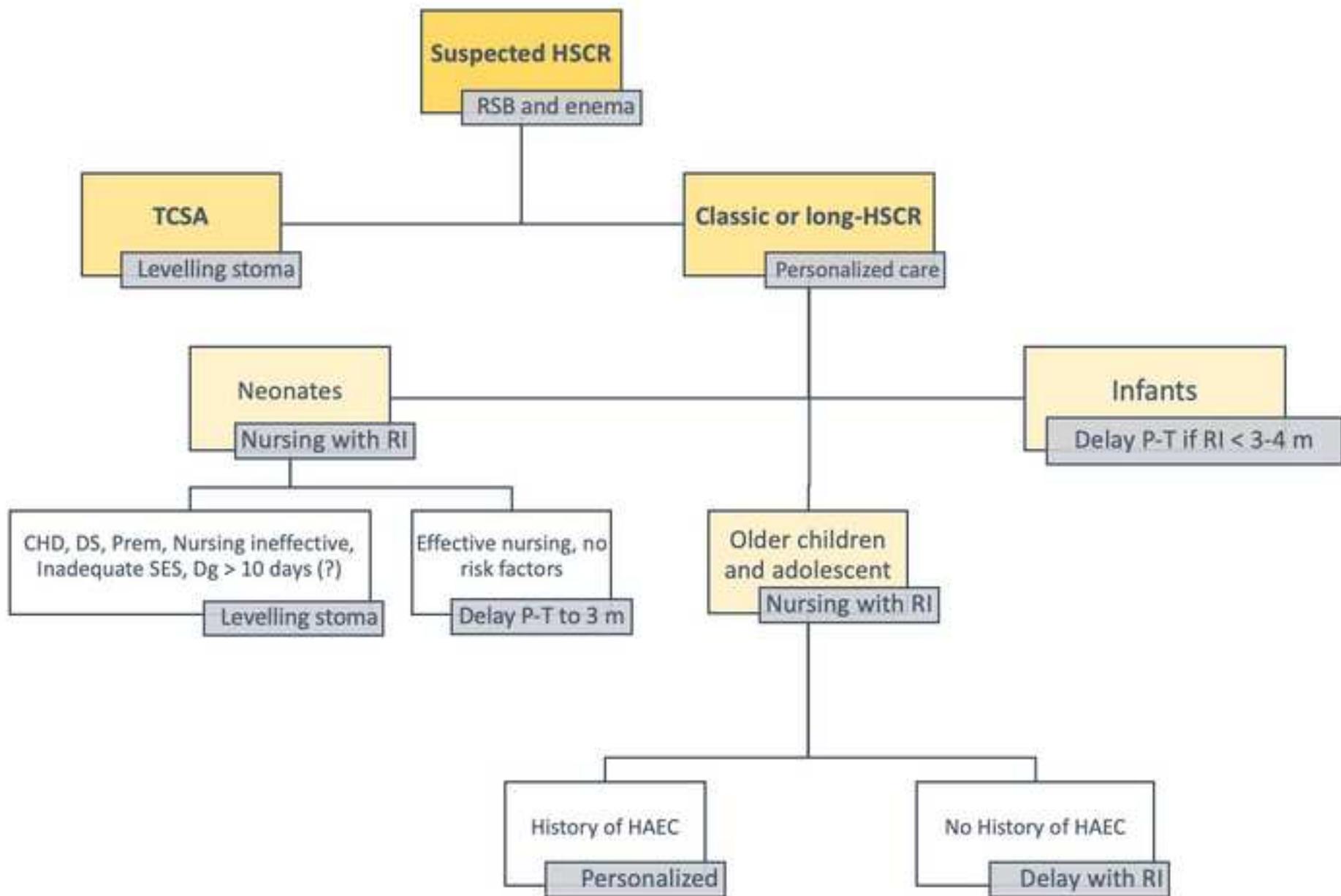
Table 1 – Most relevant papers published in the last 10 years regarding timing of surgery and preoperative HAEC determining postoperative effects. Authors worldwide addressed these issues with some flaws and BIAS limiting the reliability of the interpretation.

LEGEND TO FIGURES

Figure 1 – PRISMA diagram for systematic review

Figure 2 – Algorithm used at the Umberto Bosio Center for Digestive Diseases for defining timing for surgery according to patients' age, risk factors and present Covid-19 pandemic restrictions





Legend: HSCR = Hirschsprung; RSB = Rectal Suction Biopsy; TCSA = Total Colonic Aganglionosis; Long-HSCR = Aganglionosis confined to the right colon; Classic-HSCR = Aganglionosis confined to the left colon; Dg = Diagnosis; P-T = Pull-Through; CHD = Congenital Heart Disease; SES = Socio Economic Status; HAEC = Hirschsprung associated enterocolitis; RI = Rectal Irrigations; m = months; max = maximum

Table 1 – Most relevant papers published in the last 10 years regarding timing of surgery and preoperative HAEC determining postoperative effects. Authors worldwide addressed these issues with some flaws and BIAS limiting the reliability of the interpretation.

Ref	Year	Author	Pts	Preop HAEC	Mortality	Age at surgery	Time to surgery	BIAS	Country
5	2020	Quiroz	3635	NA	NA	< 12 months (79%)	NA	Retrospective	USA
6	2019	Zhu	198	NA	NA	3 to 12 months	NA	LOS > 10 days	China
7	2019	Lu	147	NA	NA	3 to 4 months	2 to 4 months		China
8	2019	Yulianda	61	18%	NA	NA	NA	Small series	Indonesia
9	2019	Le-Nguyen	171	15%	NA	7 weeks	6 weeks		Canada
10	2019	Pruitt	2030	8%	8%	3 months	NA	Retrospective	USA
11	2018	Freedman-Weiss	282	NA	NA	1 to 4 months	NA	Retrospective	USA
12	2017	Huang	181	15%	NA	> 2 months	NA		China
13	2017	Taguchi	1087*	17.6%	2.4%	11 months	NA	Retrospective	Japan
14	2012	Lee	44	34%	NA	NA	NA	No address surgery	Taiwan

Legend: *Pts* = patients; *HAEC* = Hirschsprung associated enterocolitis; *NA* = Not Assessed; *LOS* = Length of Stay; * = Only patients belonging to the period later than 2008 have been included; *LOS* = *Length of Stay*