Rimondi Alessandro (Orcid ID: 0000-0002-0222-7706)
Elli Luca (Orcid ID: 0000-0002-0873-0759)

Treatment Options for Gastrointestinal Bleeding Blue Rubber Bleb Nevus Syndrome: a systematic review

Alessandro Rimondi [1], Andrea Sorge [1,4], Alberto Murino [2,3], Nicoletta Nandi [1], Lucia Scaramella [4], Maurizio Vecchi [1,4], [#]Gian Eugenio Tontini [1,4] and [#]Luca Elli [4]

[#]Equally contributed

[1] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

[2] Royal Free Unit for Endoscopy, The Royal Free Hospital and University College London Institute for Liver and Digestive Health, Hampstead, London, UK

[3] Department of Gastroenterology, Cleveland Clinic London, London, United Kingdom

[4] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Gastroenterology and Endoscopy unit, Milan, Italy

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/den.14564

Guarantor of the article and address for correspondence:

Alessandro Rimondi, MD

Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Via Francesco Sforza, 25

Milan, 20122

Lombardia

Italy

alessandro.rimondi5@gmail.com

Author contributions

AR: study concept, acquisition of data, interpretation of data, drafting of the manuscript, critical revision of the manuscript, statistical analyses.

AS: acquisition of data, interpretation of data, drafting of the manuscript, critical revision of the manuscript.

AM: drafting of the manuscript, interpretation of data, critical revision of the manuscript

NN: acquisition of data, interpretation of data, critical revision of the manuscript

LS: interpretation of data, critical revision of the manuscript

MV: interpretation of data, critical revision of the manuscript

GET: study concept, interpretation of data, drafting of the manuscript, critical revision of the manuscript

LE: interpretation of data, critical revision of the manuscript

Financial support

The authors of this work declare that they did not receive any financial support.

Potential competing interests

The Authors declare no conflicts of interest.

Acknowledgments

None.

Abstract

Introduction

Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare challenging cause of gastrointestinal bleeding. We performed a systematic review of case reports and case series on BRBNS to gather information on the treatment options currently available.

Method

All studies reporting a case of BRBNS in humans were evaluated. Papers were ruled out whether CARE criteria and explanations on patient's selection, ascertainment, causality, and reporting were not respected or identified. PROSPERO 2021 CRD 42021286982.

Results

BRNBS was treated in 106 cases from 76 reports. 57.5% of the population was under 18 years old, and up to 50% of the cases reported a previous treatment. Clinical success was achieved in 98 patients (92.4%). Three main types of interventions were identified: systemic drug therapy, endoscopy and surgery. After BRBNS recurrence or previous therapy failure, systemic drug therapy emerged as a preferred second-line treatment over endoscopy ($p=0.01$), but with a higher rate of reported adverse events when compared with surgery and endoscopy ($p < 0.001$). Endoscopic treatment was associated with a higher number of required sessions to achieve complete eradication when compared with surgery ($p < 0.001$). No differences between the three main areas were found in the overall follow-up time ($p=0.19$) and in the recurrence rate ($p=0.45$).

Conclusion

Endoscopy, surgery and systemic drug therapy are feasible treatment options for BRBNS. Systemic drug therapy was the favourite second-line treatment after endoscopic failure or recurrence of BRBNS, but adverse events were more frequently reported.

Introduction

Blue rubber bleb nevus syndrome (BRBNS) is a rare disease characterized by multifocal venous malformations (VMs) that mainly involve the skin and gastrointestinal tract (GI), although it can potentially affect any organ (1,2). VMs located in the GI tract appear as soft, blue to purple nodules; they frequently lead to chronic bleeding, iron deficiency anaemia and/or acute haemorrhage (3–5) (**Figure 1**). Although aberrant VMs are often congenital and their size and number increase with age, VMs of BRBNS may develop in adult and elderly patients (6–8). Intestinal volvulus, infarction or intussusception are infrequent complications of GI tract involvement (9). To date, there is no evidence of a potential malignant evolution of VMs.

The majority of BRBNS are sporadic, although rare familial clusters are reported (10,11). Soblet et al. shed a light on the pathogenesis of this syndrome (12). A double (cis) somatic mutation in TEK, a gene encoding for TIE2 (angiopoietin-tyrosine-kinase receptor), was found in the majority of patients with BRBNS and is thought to be responsible for clinical manifestations (12). Although these findings need confirmation, mutations in TIE2 can cause endothelial cell proliferation and nevus formation through the constitutive activation of the mammalian target of the rapamycin (mTOR) pathway.

Different surgical and endoscopic techniques as well as pharmacological therapies have been proposed for the treatment of GI BRBNS (13–15). In addition to the treatment of the bleeding lesions, lifelong support with iron infusions and blood transfusions is often needed in patients with multiple lesions and different GI segments involved.

Nowadays, most of the available evidence related to BRBNS comes from case reports and small case series (15,16); this is due to the rarity of this syndrome, but also to the difficulties and associated delays to achieve a final diagnosis. Data from prospective studies are scant and no study comparing treatment options for BRBNS has been reported so far. Therefore, the true incidence of this syndrome is currently unknown.

To overcome these limitations, we conducted a systematic review of case reports and case series available in the literature, assessing the type of treatments available for patients affected by GI bleeding BRBNS-related (17). The primary aim of our research was to clarify the success rate of the medical, endoscopic and surgical treatments and to establish if there was any significant difference in terms of baseline characteristics and disease-related outcomes.

Material and Methods

Study Selection

We conducted a systematic review of studies, case series and case reports of the literature following the principles of the Joanna Briggs Institute Reviewer's Manual (18). We searched the following terms "blue" "rubber" "bleb" and "syndrome" on the EMBASE, MEDLINE and Cochrane databases up to 11th November 2021, looking for articles answering the specific question "What kind of treatments are available for patients with bleeding gastro-intestinal Blue Rubber Bleb Nevus Syndrome?". To reduce any possible retrieval bias, additional articles were identified by searching the reference lists of included studies. Rayyan software was employed for data collection and selection (19).

Inclusion and exclusion criteria

Inclusions criteria involved any publication where treatment of BRBNS gastrointestinal bleeding was described. Nominal data of the patient were included, in line with the CARE criteria (20). In addition, only publications written in English were considered. Two authors (AR, AS) searched the online databases, ruled in papers according to title and abstract, and then screened full-text articles for eligibility. Disputes between the two authors were resolved through discussion and the help of a third reviewer (NN). For each article, we recorded the study design, the year and the nation in which procedures were performed. For each patient included in the study, we recorded a set of clinical variables including sex, age, age at diagnosis, the extent of GI involvement, previous treatment, the treatment described in the paper, number of sessions

needed – in case of endoscopic or surgical treatment, clinical success (defined either as reduced need of transfusions or increased haemoglobin levels), follow up time, adverse event (AE), recurrence and death. A formal evaluation of four criteria (*i.e.,* selection, ascertainment, causality and reporting standards) of each article was performed to rule out papers that lacked significant and important clinical information. We considered a threshold of a minimum of three out of four criteria to rule in significant articles. Considering the nature of the studies, the risk of selection bias was not amendable, but it was considered in the final report. The results of our research were displayed according to PRISMA guidelines (21). This systematic review was registered on PROSPERO database (PROSPERO 2021 CRD 42021286982).

General considerations about this study methodology

It was assumed that, given the rarity of this syndrome, information was to be collected mainly from case series and case reports. However, these kinds of manuscripts present publication bias (**Figure 2**). To overcome this bias, we identified three main macro intervention populations, namely endoscopic, surgical, and pharmacological treatment. To note, when analysing the outcome of endoscopic-assisted surgery interventions, we counted them as part of the surgical macro-area, considering the overall burden of the operation. This decision was also made to preserve an adequate number of observations in the three main groups, to make statistical analysis less prone to biasing. The population of each macro area of intervention is determined by the number of patients treated, that have been published in the literature. Our process of evidence gathering is indirect, moving from what has been reported to an estimation of the true frequency of clinical characteristics, successful treatments, and outcomes of patients with BRBNS (**Figure 2**).

Statistical analyses

Data were presented in terms of numerical variables (mean ± SD or median - IQR whether a normal distribution was assumed or not) as well as categorical variables (percentage). We employed the Kruskal–Wallis one-way analysis of variance for numerical variables, as well as the Chi-squared test with Bonferroni correction for multiple comparisons for categorical variables. For comparison between two groups, the Mann-Whitney U test and the Fisher's Exact test were employed in case of respectively numerical variables or categorical variables.

R Studio version 4.0.0 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) was used for quantitative analyses.

Results

We identified a total of 499 articles through database searching. After duplicates were removed, we analysed titles and abstracts of 404 publications and 109 articles were considered for full-text evaluation. Seventy-six studies, 67 case reports and 9 case series (from 29 different countries), were finally included for quantitative analysis (**Figure 3**) (4,6,7,14,16,22-91). Data related to 106 patients who were treated for BRBNS were then extracted.

The baseline characteristics of the overall population included are summarised in **table 1**. Briefly, the population analysed included mainly paediatric patients (*i.e.* aged under 18-year-old, 57.5%) with a slight prevalence of female patients (60.3%), the most frequently affected GI tract was the small bowel, with a peak prevalence of 73.5% of ileal involvement, and half of the patients already received a treatment for GI bleeding. The most common clinical presentation was melena (53.3%), followed by iron deficiency anaemia (26.6%), suggesting an existing biological variance in the manifestation of GI bleeding.

The patients were divided into three main macro areas of treatment, namely endoscopy, surgery and drug treatment; different techniques and/or therapies belonging to the 3 macro areas of treatment are reported in **Table 2**.

Endoscopic treatments

Thirty-seven endoscopic techniques were almost equally distributed between resection and banding/looping techniques, (37.8%), haemostatic coagulation (29.7%) and sclerotizing agents (35.1%).

Up to 13.5% of the endoscopic treatments involved two combined techniques (**table 2**). When resection, banding and looping treated cases were analysed, mucosectomy was the most widely adopted treatment in 11/15 patients (73.3%), sometimes in association with other techniques (banding=1, sclerotherapy+endoloop=1, thermal haemostasis=1). Only one case of endoscopic submucosal dissection (ESD) has been reported for BRBNS. Endoloop has been reported as stand-alone endoscopic treatment in 2 cases, whereas banding was always associated with at least another treatment. Overall clinical success of resection, banding and looping was reached in 13/15 patients (86.6%). In particular, the only ESD performed was not successful (0/1, 0%) and mucosectomy was successful in 7/8 patients when applied as a stand-alone treatment (87.5%).

When sclerotizing techniques were adopted, different agents were used (alcohol=1, polidocanol=7) although in 5/13 cases the sclerotizing agent was not specified. Two patients were not treated effectively with sclerotizing techniques, namely one case of unspecified sclerotherapy and one case of polidocanol injection (2/13, 15.3%)

When haemostatic techniques were applied, thermal haemostasis and argon plasma coagulation have been described as standalone treatment in 9 patients but have been otherwise employed in association with other endoscopic techniques in other 2 cases. A case of unsuccessful treatment was disclosed in a patient who was treated with thermal haemostasis only (1/11, 9.0%).

Surgical treatments

Patients who underwent surgical procedures were mostly treated with entire or wedge resection of the affected gastrointestinal, and up one quarter of the interventions were assisted by intraoperative enteroscopy (**supplementary table 1**)

In particular, extensive surgical resections have been described in 65.5% patients whereas 34.5% patients were treated exclusively with localized such as wedge resections (80%), endoloop application (20%) and thermal haemostasis (30%) during intraoperative endoscopy.

Clinical success was reported in all patients undergoing surgery for BRBNS.

Systemic drug treatments

The mTOR inhibitors (*e.g.,* Sirolimus, Everolimus) were the most used drug therapy (82.5%), with Sirolimus almost accounting for most cases (32/33). Clinical success is reported for all the patients treated with sirolimus (100%), whereas clinical improvement was not observed in three patients respectively treated with everolimus (1/1, 100%), thalidomide (1/1, 100%) and octreotide (1/2, 50%).

Statistical analyses - baseline characteristics and outcomes

When descriptive statistics were applied to our data **(Table 3)**, the three main macro areas of treatment (*i.e.,* endoscopic treatment, surgical operations, systemic drugs) were comparable in terms of age, age at first symptoms and female-to-male ratio. Nearly all the patients had a successful clinical response to therapy, with recurrence occurring in up to one-quarter of patients, an almost null rate of death due to the diseases, and all these numbers were similar between the three cohorts.

When applying multiple comparison tests, we found a statistically significant difference between the cohort of patients treated with systemic drugs versus endoscopy in terms of patients who underwent at least one previous treatment (p=0.01). In other terms, this means that if we looked up in the existing literature what has been prescribed to patients who had a symptomatic recurrence of BRBNS lesions, articles reporting systemic drug therapy are more frequent than those reporting endoscopic-driven treatment. Also, a significant difference in terms of side effect was found in patients who received a drug treatment (43.6%) compared to surgical (7.1%) or endoscopic treatment (12.1%) (p<0.01). Notably, mucositis due to mTOR inhibitors administration is the main AE reported in the drug therapy cohort (88.2%). Additionally, when comparing the interventional group of endoscopy and surgery, a higher number of sessions is required (2 vs. 1) in the endoscopic group to achieve clinical success (p<0.01). Besides, no differences were found in terms of cases reported during an emergency scenario (*i.e.* treated urgently for haemodynamic instability and/or during admission in accident/emergency) between endoscopy and surgery.

Discussion

BRBNS is a rare disease, and this is reflected by the fact that, to the best of our knowledge, only case reports or limited case series have been reported so far. For this reason, we conducted a systematic review to gather evidence from the existing body of the literature, to provide an updated overview and comparison of the effectiveness of different therapeutical options, including medical therapy, endoscopy and surgical treatments, for patients affected by BRBNS.

Our study confirms that in the majority of cases, BRBNS is diagnosed in paediatric patients, and usually involves the small bowel. For this reason, small bowel endoscopy, including capsule endoscopy and device-assisted enteroscopy must be considered when investigating patients with suspected BRBNS incidentally found during diagnostic endoscopy or at dermatological examination. Therefore, this category of patients should be referred to small bowel tertiary referral centres with available device-assisted enteroscopy.

It appears that oral drug treatments (mostly Sirolimus) were more frequently administered as second-line therapy in patients who failed to respond to a different initial treatment, preferring the medical therapy to further endoscopic approaches. Considering our process of indirect evidence gathering, this might be justified by several hypotheses, assuming a strong positivity and publication bias. One possibility is that endoscopic techniques at the moment of recurrence fail to achieve a complete remission; another explanation could be that the effectiveness of endoscopic techniques at the moment of recurrence is not astounding, therefore those cases were not considered for publication; lastly, it is possible that the physician in charge of the patients did not believe in a significant impact of an endoscopic treatment on the recurrence.

However, we cannot rule out that these results happened only by chance and further studies are therefore needed.

Our findings also suggest that medical therapy should be preferred in patients with rebleeding caused by multiple lesions located in different parts of the GI tract, in which endoscopic or surgical treatment might be limited in the longer term, with recurrent bleedings. Although mTOR inhibitors treatment appears to be promising in these patients, their use is partially counterbalanced by AEs. To date, in the only prospective cohort study available on the treatment of BRBNS the authors enrolled 11 patients affected by BRBNS and prospectively treated them with sirolimus (adjusted to maintain through concentration of 3-10 ng/mL) achieving a significant size reduction of the VMs (22); this lead to a resolution of the GI bleeding and the anaemia in almost all the cases (10/11), with subsequent cessation of the need of blood transfusion and improvement of quality of life. On the other hand, the patients involved in this study experienced some mild self-limiting AEs, such as mucositis (81.8%), acne (27.3%) and elevated liver enzymes (18.2%)(22).

We also showed that overall clinical success was achieved in 92% (98/106); only one case of death was reported in a paediatric patient due to failure to control the disease with subsequent massive gastrointestinal haemorrhage (23). This optimistic result must be taken with caution as it entails positivity and publication bias. In fact, we expect articles reporting a positive outcome to be more commonly published, introducing a skewness in the evidence.

BRBNS remains a difficult entity to properly ascertain due to its rarity and its scattered geographical distribution. Due to the lack of perspective multicentre trials and high-quality

evidence, it is difficult to propose a shared treatment algorithm. For example, invasive treatments (i.e. endoscopy and surgery) as a first-line approach, with sirolimus as a second-line treatment, can be considered based on concerns over sirolimus life-long treatment and its side-effects, which may significantly impact on quality of life. On the opposite, a sirolimus-based first-line therapy could be suggested in those patients with countless VMs or when there are concerns over the invasiveness of surgical or endoscopic techniques (24).

The main limitation of our study is the already discussed nature of the articles analysed (*i.e.,* case series and case reports). In this sense, all the statistically significant differences we have noted in terms of clinical variables and outcomes should not be considered as real existing differences between treatments. That could only be evident with retrospective cohort studies or (even better) with randomized controlled trials. Instead, our results are quantitative differences in reporting, and we drew conclusions by indirect demonstration. Another potential limitation is that, due to data paucity, we did not compare different kinds of techniques in the same macro area of treatments (*e.g.,* loop technique vs. argon plasma coagulation). As this systematic review relies on case reports and case series coming from centres with different expertise, the results should be considered with a very low/low grade of evidence.

Conclusion

Endoscopy, surgery and systemic drug therapy are feasible treatment options for BRBNS, but the best treatment options and therapy algorithms are not known yet. Systemic drug therapy was the favourite second-line treatment after endoscopic failure or recurrence of BRBNS, but adverse events were more frequently reported. Therefore, prospective and multicentres studies are indeed warranted, including longer follow-up time, to confirm the best treatment options for patients with BRBNS.

Legend

Figure 1 – On the left part of the image (A), video capsule endoscopy of blue rubber bleb nevus in the jejunum. On the right part of the image (B), the same patient being treated for bleeding blue rubber bleb nevus in the jejunum with argon plasma coagulation.

Figure 2 – Proposed scheme for representing actual evidence regarding Blue Rubber Bleb Nevus Syndrome and mechanism of evidence gathering.

Figure 3 – PRISMA Flow diagram for systematic review.

Table 1 – Baseline characteristics of the cohort of cases.

Table 2 – Specific reported treatment divided by macro-area.

Table 3 – Difference in reporting between clinical baseline variables and outcomes in the three main areas.

Supplementary table 1 – Surgery treatments available for Blue Rubber Bleb Nevus Syndrome for each GI site.

References

1. Jin XL, Wang ZH, Xiao XB, Huang LS, Zhao XY. Blue rubber bleb nevus syndrome: A case report and literature review. World J Gastroenterol 2014; 20: 17254-9.

2. Wynford-Thomas R, Johnston A, Halpin S, Hamandi K. Rarities in neurology: Blue rubber bleb naevus syndrome. Pract Neurol 2014; 14: 360-2.

3. Lybecker MB, Stawowy M, Clausen N. Case report: Blue rubber bleb naevus syndrome: A rare cause of chronic occult blood loss and iron deficiency anaemia. BMJ Case Rep 2016; 2016: bcr2016216963.

4. Tang X, Gao J, Yang X, Guo X. A 10-year delayed diagnosis of blue rubber bleb nevus syndrome characterized by refractory iron-deficiency anemia: A case report and literature review. Medicine (Baltimore) 2018; 97: E10873

5. Li A, Chen FX, Li YQ. An unusual cause of recurrent melena. Gastroenterology 2019; 157: 311-2.

6. Chen W, Chen H, Shan G et al. Blue rubber bleb nevus syndrome: Our experience and new endoscopic management. Medicine (Baltimore) 2017; 96: E7792.

7. Winkler J, Bonnet M, Haffner A et al. Blue rubber bleb nevus syndrome: An unusual cause of intestinal bleeding in the elderly. Endoscopy 2022; 54: E53-E4.

8. Monrigal E, Gallot D, James I, Hameury F, Vanlieferinghen P, Guibaud L. Venous malformation of the soft tissue associated with blue rubber bleb nevus syndrome: Prenatal imaging and impact on postnatal management. Ultrasound Obstet Gynecol 2009; 34: 730-2.

9. Esposito C, Giurin I, Farina A et al. Blue rubber bleb nevus: An uncommon cause of intestinal intussusception. Eur J Pediatr 2012; 171: 1139-40.

10. Kisu T, Yamaoka K, Uchida Y et al. A case of blue rubber bleb nevus syndrome with familial onset. Gastroenterol Jpn 1986; 21: 262-6.

11. Carvalho S, Barbosa V, Santos N, Machado E. Blue rubber-bleb nevus syndrome: Report of a familial case with a dural arteriovenous fistula. AJNR Am J Neuroradiol 2003; 24: 1916-8.

12. Soblet J, Kangas J, Nätynki M et al. Blue rubber bleb nevus (brbn) syndrome is caused by somatic tek (tie2) mutations. J Invest Dermatol 2017; 137: 207-16.

13. Xia H, Wu J, Huang Y. Blue rubber bleb nevus syndrome: A single-center case series in 12 years. Transl Pediatr 2021; 10: 2960-71.

14. Tang XY, He CH, Liao Z. Successful endoscopic diagnosis and treatment of blue rubber bleb nevus syndrome. Endoscopy 2021; 53: 118-9.

15. Fishman SJ, Smithers CJ, Folkman J et al. Blue rubber bleb nevus syndrome: Surgical eradication of gastrointestinal bleeding. Ann Surg 2005; 241: 523-8.

16. Isoldi S, Belsha D, Yeop I et al. Diagnosis and management of children with blue rubber bleb nevus syndrome: A multi-center case series. Dig Liver Dis 2019; 51: 1537-46.

17. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018; 23: 60-3.

18. The Joanna Briggs I. Joanna briggs institute reviewers' manual: 2014 edition, The Joanna Briggs Institute, 2014.

19. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan - a web and mobile app for systematic reviews. Syst Rev 2016: 5:10-5.

20. Gagnier JJ, Kienle G, Altman DG et al. The care guidelines: Consensus-based clinical case reporting guideline development. BMJ Case Rep 2013; 2013: bcr2013201554.

21. Page MJ, McKenzie JE, Bossuyt PM et al. The prisma 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021; 10: 89.

22. Yokoyama M, Ozeki M, Nozawa A, Usui N, Fukao T. Low-dose sirolimus for a patient with blue rubber bleb nevus syndrome. Pediatr Int 2020; 62: 112-3.

23. Weiss D, Teichler A, Hoeger PH. Long-term sirolimus treatment in blue rubber bleb nevus syndrome: Case report and review of the literature. Pediatr Dermatol 2021; 38: 464-8.

24. Hu Z, Lin X, Zhong J et al. Blue rubber bleb nevus syndrome with the complication of intussusception: A case report and literature review. Medicine (Baltimore) 2020; 99: E21199.

25. Lazaridis N, Murino A, Koukias N, Kiparissi F, Despott EJ. Blue rubber bleb nevus syndrome in a 10-year-old child treated with loop ligation facilitated by double-balloon enteroscopy. VideoGIE 2020; 5: 412-4.

26. Gil MF, Serrano López P, García EG. Successful management of anemia with sirolimus in blue rubber bleb nevus syndrome: Case report and update. Rev Esp Enferm Dig 2019; 111: 643-7.

27. Kumei T, Toya Y, Shiohata T et al. Gastrointestinal: Endoscopic injection sclerotherapy for

duodenal vascular malformation in blue rubber bleb nevus syndrome. J Gastroenterol Hepatol 2019; 34: 963.

28. Malafaia MC, Heissat S, Jacob P et al. Blue rubber bleb nevus syndrome: Endoscopic treatment with sclerotherapy during double-balloon enteroscopy in a 9-year-old boy. Endoscopy 2019; 51: E98-E100.

29. Nakajima H, Nouso H, Urushihara N et al. Blue rubber bleb nevus syndrome with long-term follow-up: A case report and review of the literature. Case Rep Gastrointest Med 2018; 2018: 1-7.

30. Martinez CAR, Rodrigues MR, Sato DT et al. Blue rubber bleb nevus syndrome as a cause of lower digestive bleeding. Case Rep Surg 2014; 2014: 1-4.

31. Aravindan U, Ganesan R, Thamarai Kannan M. Surgery for blue rubber bleb nevus syndrome-a case report. Indian J Surg 2018; 80: 272-4.

32. Li Z, Yuan H, Yu D et al. The surgery for blue rubber bleb nevus syndrome. Ann Med Surg (Lond) (2012) 2015; 5: 93-6.

33. Dwivedi M, Misra SP. Blue rubber bleb nevus syndrome causing upper gi hemorrhage: A novel management approach and review. Gastrointest Endosc 2002; 55: 943-6.

34. Ogu UO, Abusin G, Abu-Arja RF, Staber JM. Successful management of blue rubber bleb nevus syndrome (brbns) with sirolimus. Case Rep Pediatr 2018; 2018: 1-5.

35. Akyuz C, Susam-Sen H, Aydin B. Blue rubber bleb nevus syndrome: Promising response to sirolimus. Indian Pediatr 2017; 54: 53-4.

36. Salloum R, Fox CE, Alvarez-Allende CR et al. Response of blue rubber bleb nevus syndrome to sirolimus treatment. Pediatr Blood Cancer 2016; 63: 1911-4.

37. Zhou J, Zhao Z, Sun T et al. Efficacy and safety of sirolimus for blue rubber bleb nevus syndrome: A prospective study. Am J Gastroenterol 2021; 116: 1044-52.

38. Xu Y, Wu Y, Dai Z, Xia F, Xu F. A combination of single-balloon enteroscopy-assisted laparoscopy and endoscopic mucosal resection for treating gastrointestinal venous malformations in blue rubber bleb nevus syndrome: A case report. BMC Gastroenterol 2020; 20: 182.

39. Dieckmann K, Maurage C, Faure N et al. Combined laser-steroid therapy in blue rubber bleb nevus syndrome: Case report and review of the literature. Eur J Pediatr Surg 1994; 4: 372-4.

40. Wu C, Tan Q, Zhang Q, Hu B. Successful endoscopic resection of blue rubber bleb nevus syndrome in the stomach using a snare. Am J Gastroenterol 2017; 112: 1494.

41. Ertem D, Acar Y, Kotiloglu E, Yucelten D, Pehlivanoglu E. Blue rubber bleb nevus syndrome. Pediatrics 2001; 107: 418-21.

42. Carr MM, Jamieson CG, Lal G. Blue rubber bleb nevus syndrome. Can J Surg 1996; 39: 59-62.

43. Guo W, Peng Z, Tang X, Zhao Z, Liu Z. Endoscopic management of blue rubber bleb nevus syndrome: A case report. Exp Ther Med 2013; 6: 1159-62.

44. Ning S, Zhang Y, Zu Z, Mao X, Mao G. Enteroscopic sclerotherapy in blue rubber bleb nevus syndrome. Pak J Med Sci 2015; 31: 226-8.

45. Arena M, Virdis M, Morandi E et al. Blue rubber bleb nevus syndrome: Combined surgical and endoscopic treatment. Endoscopy 2015; 47 Suppl 1 UCTN: E372-E3.

46. Yuksekkaya H, Ozbek O, Keser M, Toy H. Blue rubber bleb nevus syndrome: Successful treatment with sirolimus. Pediatrics 2012; 129: E1080-E4.

47. Boente MDC, Cordisco MR, Frontini MDV, Asial RA. Blue rubber bleb nevus (bean syndrome): Evolution of four cases and clinical response to pharmacologic agents. Pediatr Dermatol 1999; 16: 222-7.

48. Wang KL, Ma SF, Pang LY et al. Sirolimus alternative to blood transfusion as a life saver in blue rubber bleb nevus syndrome: A case report. Medicine (Baltimore) 2018; 97: E9453.

49. Shimada S, Namikawa K, Maeda K et al. Endoscopic polypectomy under laparotomy throughout the alimentary tract for a patient with blue rubber bleb nevus syndrome. Gastrointest Endosc 1997; 45: 423-7.

50. Ng EKW, Cheung FKY, Chiu PWY. Blue rubber bleb nevus syndrome: Treatment of multiple gastrointestinal hemangiomas with argon plasma coagulator. Dig Endosc 2009; 21: 40-2.

51. Teixeira MG, Perini MV, Marques CFS, Habr-Gama A, Kiss D, Gama-Rodrigues JJ. Blue rubber bleb nevus syndrome: Case report. Rev Hosp Clin Fac Med Sao Paulo 2003; 58: 109-12.

52. Hasosah MY, Abdul-Wahab AA, Bin-Yahab SA et al. Blue rubber bleb nevus syndrome: Extensive small bowel vascular lesions responsible for gastrointestinal bleeding. J Paediatr Child Health 2010; 46: 63-5.

53. Dòmini M, Aquino A, Fakhro A et al. Blue rubber bleb nevus syndrome and gastrointestinal

haemorrhage: Which treatment? Eur J Pediatr Surg 2002; 12: 129-33.

54. Wang Z, Yang X, Wu L et al. Blue rubber bleb nevus syndrome: Treatment of lesions in the small intestine with repeated injection of lauromacrogol. Gastrointest Endosc 2015; 81: 1274-5.

55. Shin SH, Chae HS, Ji JS et al. A case of blue rubber bleb nevus syndrome. Korean J Intern Med 2008; 23: 208-12.

56. Place RJ. Blue rubber bleb nevus syndrome: A case report with long-term follow-up. Military Medicine (Baltimore) 2001; 166: 728-30.

57. Menegozzo CAM, Novo FdCF, Mori ND, Bernini CdO, Utiyama EM. Postoperative disseminated intravascular coagulation in a pregnant patient with blue rubber bleb nevus syndrome presenting with acute intestinal obstruction: Case report and literature review. Int J Surg Case Rep 2017; 39: 235-8.

58. Marakhouski K, Sharafanovich E, Kolbik U et al. Endoscopic treatment of blue rubber bleb nevus syndrome in a 4-year-old girl with long-term follow-up: A case report. World J Gastrointest Endosc 2021; 13: 90-6.

59. Hansen LF, Wewer V, Pedersen SA, Matzen P, Paerregaard A. Severe blue rubber bleb nevus syndrome in a neonate. Eur J Pediatr Surg 2009; 19: 47-9.

60. Wu C, Luo R, Li X, Hu B. Endoscopic management of blue rubber bleb nevus syndrome in the colon with hemostatic clamp and snare. Endoscopy 2017; 49: E149-E50.

61. Ünlüsoy Aksu A, Sari S, Eğritaş Gürkan Ö, Dalgiç B. Favorable response to sirolimus in a child

with blue rubber bleb nevus syndrome in the gastrointestinal tract. J Pediatr Hematol Oncol 2017; 39: 147-9.

62. Rubio-Mateos JM, Tojo-González R, Pérez-Cuadrado-Robles E. Endoscopic mucosal resection by double-balloon enteroscopy can be an alternative in small bowel venous malformations. Dig Endosc 2018; 30: 789.

63. Aron J, Couturier A, Sinayoko L, Duedal V, Ridel C, Touzot M. An unusual cause of gastrointestinal bleeding in a hemodialysis patient. Hemodial Int 2018; 22: E60-E2.

64. Warner B, Butt A, Cairns S. Sirolimus is a successful treatment for recurrent iron deficiency anaemia in blue rubber bleb naevus syndrome. J Pediatr Gastroenterol Nutr 2015; 60: e49-e50.

65. Ferrés-Ramis L, Knöpfel N, Salinas-Sanz JA, Martín-Santiago A. Rapamycin in the treatment of blue rubber bleb nevus syndrome. Actas Dermosifiliogr (Engl Ed) 2015; 106: 137-8.

66. Takasumi M, Hikichi T, Takagi T et al. Endoscopic therapy for esophageal hematoma with blue rubber bleb nevus syndrome. World J Gastrointest Endosc 2014; 6: 630-4.

67. Jin J, Pan J, Zhu L. Therapy for hemangiomas of blue rubber bleb nevus syndrome in the small intestine with single balloon endoscopy. Dig Endosc 2015; 27: 780.

68. Choi KK, Kim JY, Kim MJ et al. Radical resection of intestinal blue rubber bleb nevus syndrome. J Korean Surg Soc 2012; 83: 316-20.

69. Gonzalez D, Elizondo BJ, Haslag S et al. Chronic subcutaneous octreotide decreases gastrointestinal blood loss in blue rubber-bleb nevus syndrome. J Pediatr Gastroenterol

Nutr 2001; 33: 183-8.

70. Nakagawara G, Asano E, Kimura S, Akimoto R, Miyazaki I. Blue rubber bleb nevus syndrome: Report of a case. Dis Colon Rectum 1977; 20: 421-7.

71. Deng Z-H, Xu C-D, Chen S-N. Diagnosis and treatment of blue rubber bleb nevus syndrome in children. World J Pediatr 2008; 4: 70-3.

72. Mavrogenis G, Coumaros D, Tzilves D et al. Cyanoacrylate glue in the management of blue rubber bleb nevus syndrome. Endoscopy 2011; 43 Suppl 2 UCTN> E291-E2.

73. Cardoso H, Dias JA, Silva M et al. 'Education and imaging. Gastrointestinal: Successful treatment with sirolimus of a patient with blue rubber bleb nevus syndrome. J Gastroenterol Hepatol 2016; 31: 519.

74. Bak YT, Chil Hwan O, Jin Ho K, Chang Hong L. Blue rubber bleb nevus syndrome: Endoscopic removal of the gastrointestinal hemangiomas. Gastrointest Endosc 1997; 45: 90-2.

75. Özgönenel B, Martin A. Low-dose sirolimus controls recurrent iron deficiency in a patient with blue rubber bleb nevus syndrome. Pediatr Blood Cancer 2015; 62: 2054-5.

76. Kopáčová M, Tachecí I, Koudelka J, Králová M, Rejchrt S, Bureš J. A new approach to blue rubber bleb nevus syndrome: The role of capsule endoscopy and intra-operative enteroscopy. Pediatr Surg Int 2007; 23: 693-7.

77. Campos-Murguía A, Zamora-Nava LE. An endoscopic multimodal approach in a patient with blue rubber bleb nevus syndrome and acute bleeding. Endoscopy 2021; 53: E338-E9.

78. Morris L, Lynch PM, Gleason WA, Schauder C, Pinkel D, Duvic M. Blue rubber bleb nevus

syndrome: Laser photocoagulation of colonic hemangiomas in a child with microcytic anemia. Pediatr Dermatol 1992; 9: 91-4.

79. Raman VS, Bhatnagar V. Blue rubber bleb nevus syndrome--role of aggressive surgical resection. Trop Gastroenterol 2015; 36: 125-7.

80. Ng WT, Kong CK. Argon plasma coagulation for blue rubber bleb nevus syndrome in a female infant. Eur J Pediatr Surg 2003; 13: 137-9.

81. Grammatopoulos A, Petraki K, Katsoras G. Combined use of band ligation and detachable snares (endoloop) in a patient with blue rubber bleb nevus syndrome. Ann Gastroenterol 2013; 26: 264-6.

82. Kanai M, Noike M, Masaki C et al. Severe gastrointestinal bleeding during pregnancy in a case of blue rubber bleb nevus syndrome. Semin Thromb Hemost 2005; 31: 284-9.

83. Shahed M, Hagenmuller F, Rosch T et al. A 19-year-old female with blue rubber bleb nevus syndrome. Endoscopic laser photocoagulation and surgical resection of gastrointestinal angiomata. Endoscopy 1990; 22: 54-6.

84. Suksamanapun N, Trakarnsanga A, Akaraviputh T. Blue rubber bleb nevus syndrome. Endoscopy 2011; 43 Suppl 2 UCTN:E411-E2

85. Chen SM, Tsao TF, Lee HL. A rare cause of chronic anemia and recurrent bowel obstruction. Gastroenterology 2018; 154: E4-E7.

86. Lockie E, Liyanage R, Brown G, Miller F. Perforation following enteroscopic treatment of blue rubber bleb naevus syndrome. ANZ J Surg 2021; 91: E208-E9.

87. Emami MH, Haghdani S, Tavakkoli H, Mahzouni P. Endoscopic polypectomy resection of blue rubber bleb nevus lesions in small bowel. Indian J Gastroenterol 2008; 27: 165-6.

88. Robertson JO, Kung VL, Utterson EC, White FV, White AJ, Vogel AM. Blue rubber bleb nevus syndrome without cutaneous manifestations: A rare presentation of chronic anemia. J Pediatr Surg Case Rep 2014; 2: 70-2.

89. Arguedas MR, Wilcox CM. Blue rubber bleb nevus syndrome. Gastrointest Endosc 1999; 50: 544.

90. De Bona M, Bellumat A, De Boni M. Capsule endoscopy for the diagnosis and follow-up of blue rubber bleb nevus syndrome. Dig Liver Dis 2005; 37: 451-3.

91. Mat Johar F, Wan Sulaiman WA, Mat Saad AZ, Basiron N, Sahid NA. Blue rubber bleb nevus syndrome in a malay girl: A case report and literature review. Int J Surg Case Rep 2020; 72: 202-6.

92. Echenique-Elizondo M. Chronic digestive bleeding in blue rubber-bleb nevus (bean syndrome). J Am Coll Surg 2003; 196: 816.

Baseline Characteristics	Patients number = 106
Age (median, years)	14.0 (Interquartile range 8.0 – 20.0)
Female (%)	64 (60.3)
Patients aged under 18-year-old (%)	61 (57.5)
Clinical presentation (%) [#]	Melena 40 (53.3) Iron deficiency anemia 20 (26.6) Non specified overt bleeding 7 (9.3) Proctorrhagia 5 (6.6) Hematemesis 3 (4)
Affected GI[§] tract (%) *	Oesophagus 3 (3.6) Stomach 42 (50.6) Duodenum 57 (68.6) Jejunum 57 (68.6) Ileum 61 (73.5) Colon 52 (62.6) Rectum 5 (6.9) *Not acquired 23*
Previous treatment (%)	Any treatment 53 (50.0) Endoscopy 29 (27.3) Surgery 20 (18.8) Drugs 11 (10.4)

Table 1. Baseline characteristics of patients with Bleeding Blue Rubber Bleb Nevus Syndrome

[#] available in 75 cases

[§] GI = gastrointestinal

* available in 83 cases

Table 2. Specific treatments for Bleeding Blue Rubber Bleb Nevus Syndrome.

Endoscopy procedures n = 37	**No. (%)**
Single treatment	
Snare mucosectomy	8 (21.6)
Polidocanol injection	6 (16.2)
Sclerotherapy not specified	5 (13.5)
Endoloop	2 (5.4)
Thermal haemostasis	3 (8.1)
Alcohol injection	1 (2.7)
APC[#]	6 (16.2)
ESD[§]	1 (2.7)
Combined therapy	
APC[#] + polidocanol	1 (2.7)
Banding + endoloop	1 (2.7)
Banding + snare mucosectomy	1 (2.7)
Sclerotherapy + snare mucosectomy + endoloop	1 (2.7)
Thermal haemostasis + Snare mucosectomy	1 (2.7)
Surgery procedures n = 29	**No. (%)**
SB[@] resection	9 (31.0)
SB[@] resection + SB wedge excision	3 (10.3)
SB[@] wedge excision + Colon wedge resection	2 (6.9)
Intraoperative enteroscopy thermal haemostasis + surgical SB[@] resection	2 (6.9)
Colon resection	1 (3.4)
Colon resection + SB resection + SB[@] wedge excision	1 (3.4)
Gastrotomy + SB resection + colotomy	1 (3.4)
Gastrotomy + SB resection + SB wedge resection	1 (3.4)
Haemorrhoidectomy	1 (3.4)
Intraoperative enteroscopic snare mucosectomy	1 (3.4)
Proctocolectomy	1 (3.4)
SB[@] resection + intraoperative enteroscopy with snare mucosectomy	1 (3.4)
SB[@] resection + SB wedge excision + endoloop	1 (3.4)
SB[@] resection + sclerotherapy + endoloop	1 (3.4)
SB[@] wedge excision + endoloop	1 (3.4)
SB[@] wedge excision + thermal haemostasis	1 (3.4)
Wedge excision	1 (3.4)
Systemic drug treatment n = 40	**No. (%)**
Sirolimus	32 (80.0)
IFN-alfa + steroids	2 (5.0)
Methlprednisolone	2 (5.0)
Octreotide	2 (5.0)
Everolimus	1 (2.5)
Thalidomide	1 (2.5)

[#] APC = argon plasma coagulation

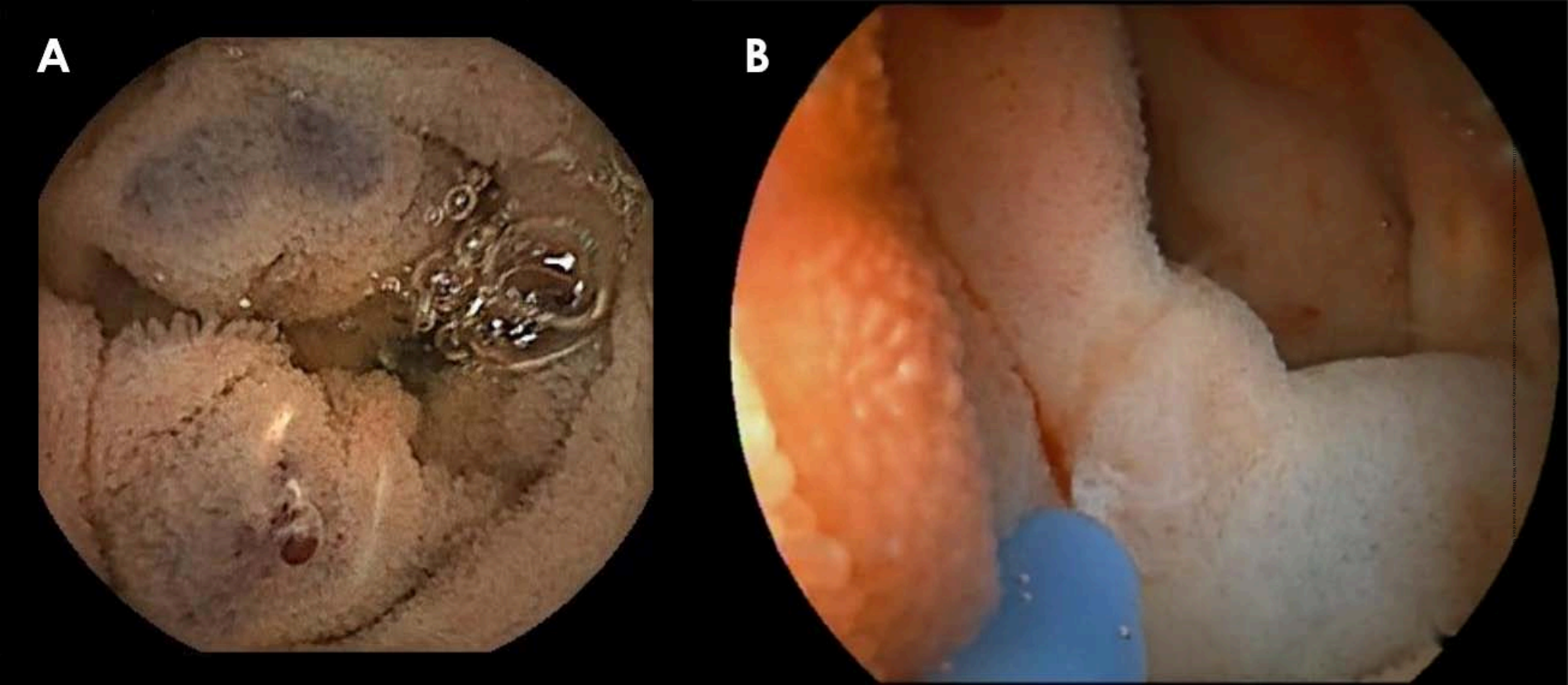
[§] ESD = endoscopic submucosal dissection

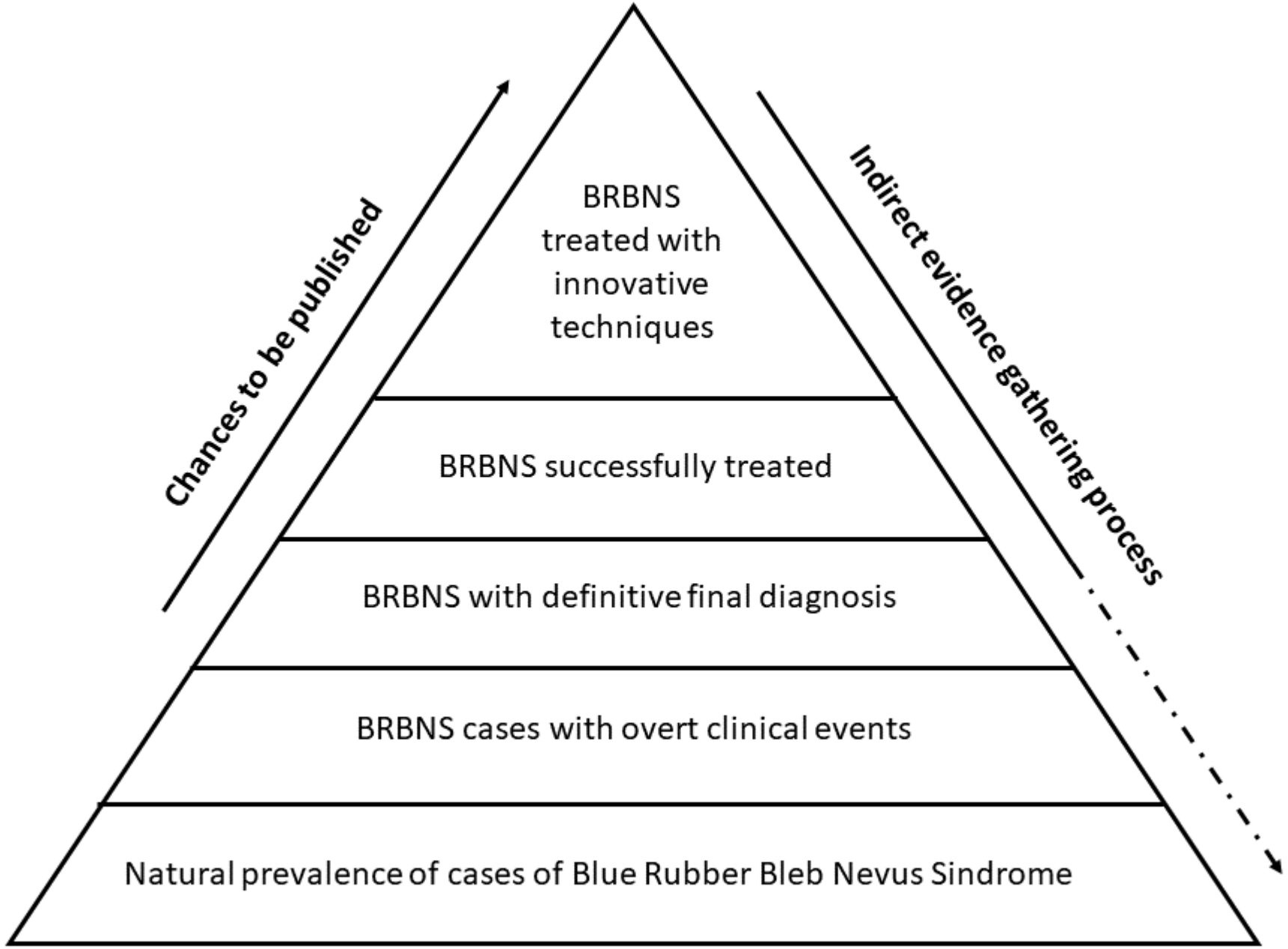
[@] SB = small bowel

Table 3. Difference in reporting between clinical baseline variables and outcomes in the three main treatment choices for Bleeding Blue Rubber Bleb Nevus Syndrome.

§ IQR = interquartile range

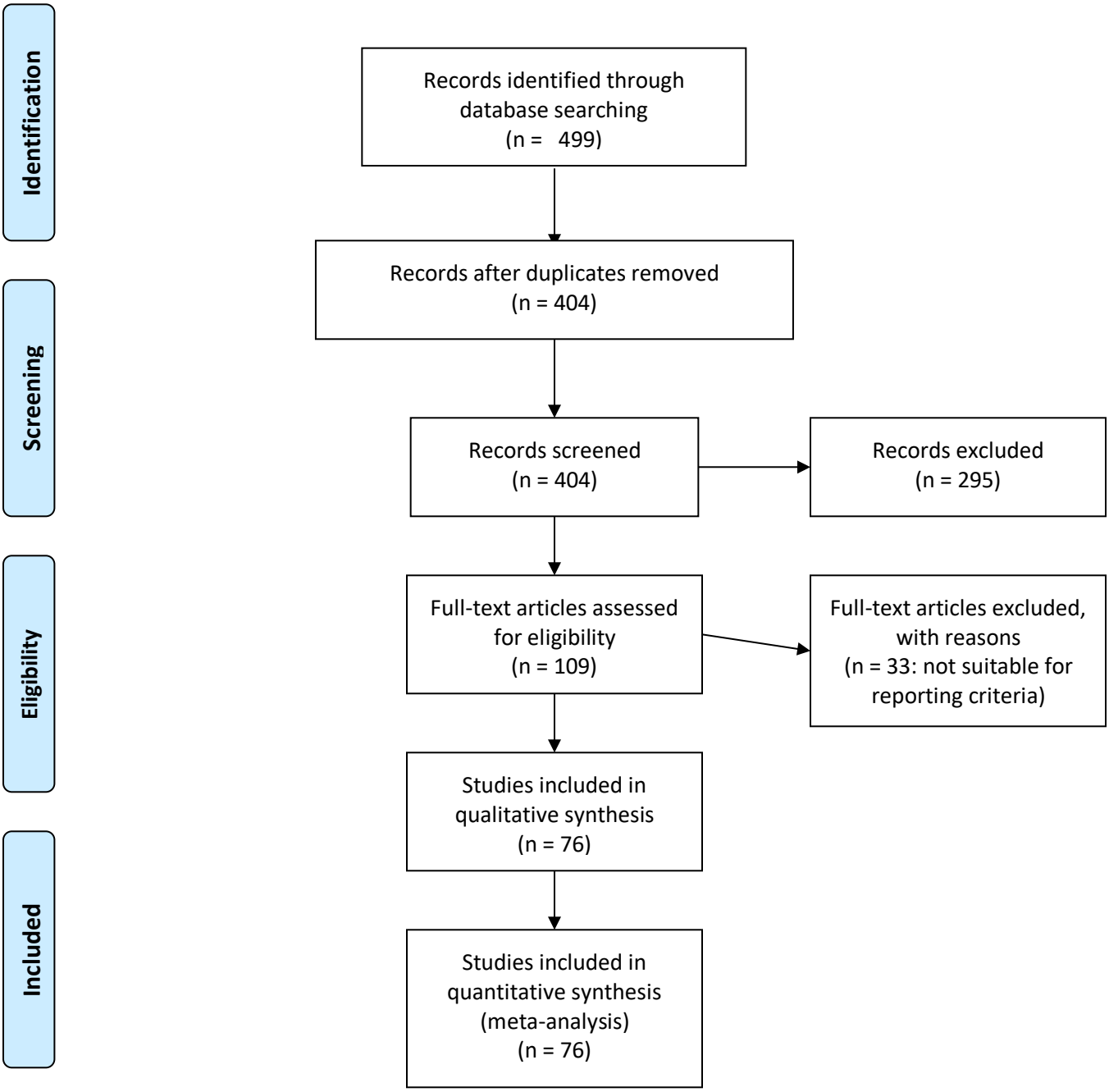
	Endoscopy (E) n = 37	Surgery (S) n = 29	Drugs (D) n = 40	P-value
Age (median, years)	16.5 (IQR§ 8.5 – 21.5)	15.0 (IQR§ 11.0 – 22.0)	11.5 (IQR§ 6.0 – 18.0)	0.14
Age at first symptoms (median, years)	10.0 (IQR§ 4.0 – 15.5)	10.0 (IQR§ 5.75 – 13.25)	5.0 (IQR§ 3.0 – 11.0)	0.12
Female (%)	18 / 37 (48.6)	23 / 29 (79.3)	23 / 40 (57.5)	E vs. S = 0.06 E vs. D = 0.58 S vs. D = 0.15
Pediatric patients (%)	17 / 37 (45.9)	13 / 29 (44.8)	14 / 40 (35.0)	E vs. S = 1.00 E vs. D = 0.85 S vs. D = 0.85
Previous treatment (%)	12 / 37 (32.4)	14 / 29 (48.3)	27 / 40 (67.5)	E vs. S = 0.29 **E vs. D = 0.01** S vs. D = 0.26
Clinical success (%)	32 / 37 (86.4)	29 / 29 (100.0)	37 / 40 (92.5)	E vs. S = 0.33 E vs. D = 0.62 S vs. D = 0.54
Follow up time (median, months)	12.0 (IQR 6.0 – 28.5)	24.0 (IQR 12.0 – 45.0)	16.0 (IQR 12.0 – 21.5)	0.19
Recurrence (%)	6 / 37 (16.2)	2 / 29 (6.7)	7 / 40 (17.5)	E vs. S = 0.66 E vs. D = 1.00 S vs. D = 0.66
Adverse event (%)	4 / 39 (10.1)	2 / 27 (7.4)	18 / 40 (45.0)	E vs. S = 0.91 **E vs. D = < 0.01** **S vs. D = < 0.01**
Death (%)	0 / 39 (0.0)	0 / 29 (0.0)	1 / 40 (2.5)	E vs. S = NA E vs. D = 1.00 S vs. D = 1.00
Session needed (median)	2 (IQR§ 1 – 4)	1 (IQR§ 1 – 1)	NA	**< 0.01**
Emergency setting (%)	7 / 30 (23.3)	6 / 29 (20.6)	NA	0.89


A
B



PRISMA 2009 Flow Diagram_WG3_PEO4

PubMed and Embase were searched for articles published up to December the 17th 2021, for this specific question ("What are the treatment options for Blue Rubber Bleb Nevus Syndrome?") resulting in 499 manuscripts according to the following search strategy: (Blue Rubber Bleb Nevus)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 3 - PRISMA Flow diagram for systematic review