Journal of Pediatric Gastroenterology and Nutrition, Publish Ahead of Print
DOI : 10.1097/MPG.0000000000002981

ANTIBIOTIC PROPHYLAXIS FOR PERCUTANEOUS ENDOSCOPIC GASTROSTOMY IN CHILDREN: A RANDOMISED CONTROLLED TRIAL

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Conflict of Interest Disclosures: The authors have no conflicts of interest to declare.
Funding/Support: No funding was secured for this study.
Trial Registration: Clinical Trial Gov., NCT 01870167, www.clinicaltrials.gov, individual participant data will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to giovanni.dinardo@uniroma1.it

Abstract

Objectives: Paediatric studies on the role of antibiotic prophylaxis in the prevention of postoperative infections in children undergoing percutaneous endoscopic gastrostomy (PEG) are lacking. The aim of this study was to assess if a single dose of co-amoxiclav before PEG can decrease the rate of peristomal wound and systemic infection in children.

Methods: In this prospective, randomised, double blind, multicenter trial, children undergoing PEG were randomized to antibiotic prophylaxis with co-amoxiclav versus placebo and the rate of local and systemic infections were assessed.

Results: Of the 106 patients considered for inclusion, 49 patients were randomized. In the per protocol analysis, the occurrence of wound infection was 5 % (1/20) in the antibiotic group and 21% (4/19) in the placebo group [p= 0.13, 16% difference in proportions, OR 0.19, 95% CI 0.02-1.9]. The occurrence of systemic infection was 9% (2/22) in the antibiotic group and 27.2% (6/25) in the placebo group [p=0.17, 18% difference in proportions, OR 0.32, 95% CI 0.06-1.80%]. Similar results were obtained in intention to treat analysis. Interestingly, the overall infection rate was significantly higher in the placebo group as compared to the antibiotic group (40% vs 13,6%; p =0.04) and the duration of hospital stay was significantly longer in the placebo group as compared to the antibiotic group (4.4±1.6 vs 3.5±1.05; p =0.02). The number-needed-to-treat (NTT) to prevent one peristomal infection on average are 6.7 patients.

Conclusions: A preoperative dose of co-amoxiclav reduces the overall infection rate and the duration of hospital stay. Our data suggest that antibiotic prophylaxis should be recommended in every children undergoing PEG placement.

Key words: peristomal wound infection, endoscopy, children.

What is known

- Antibiotic prophylaxis is a well-established strategy to reduce peristomal wound infection rate in adult population.
- Observational studies in paediatric population showed that antibiotic prophylaxis did not decrease infectious complications in children undergoing percutaneous endoscopic gastrostomy (PEG).

What is new

- This is the first RCT in children showing that a preoperative single dose of co-amoxiclav reduces the overall infection rate and the duration of hospital stay.
- Antibiotic prophylaxis should be recommended in every children undergoing PEG placement.

Introduction

Percutaneous Endoscopic Gastrostomy (PEG) is a common endoscopic procedure in children, performed to avoid malnutrition in various pathological conditions that impair swallowing, such as neurological disorders, dysphagia, trauma or malignant disease (1).

Despite generally safe, PEG placement is associated with intra and postoperative complications both in the adult and in the paediatric population (2,3). As a consequence of malnutrition and comorbidities, patients undergoing PEG placement are often vulnerable to infection, which is the most common complication following PEG with an incidence between 4% and 30% (4,5). This complication often requires treatment with systemic antibiotics, intensive local wound care, and adjustment of the PEG catheter if fitted too tightly. Sometimes wound infections can evolve into necrotising fasciitis, a devastating complication with high mortality (6). Antibiotic prophylaxis is a well-established strategy to reduce peristomal wound infection rate in adult population and is strongly recommended (7). However, paediatric studies concerning the role of antibiotic prophylaxis in the prevention of such complications are limited. Few retrospective and prospective observational studies in paediatric population showed that antibiotic prophylaxis did not decrease infectious complications in children undergoing PEG (8-10). Despite there are no randomized control trials on antibiotic prophylaxis at time of PEG insertion in children, the 2015 position paper of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (1) stated that antibiotics given at the time of PEG insertion reduced postoperative infection rates, but that advice was based on the expert opinion and personal practice of the authors and on the Cochrane review (7), which only considered the evidence in adults. Although guidelines are currently lacking, antibiotic prophylaxis prior to PEG in children seems to be common practice (11). However, the results from studies in adults should not be extrapolated to the paediatric population. Indeed, the widespread use of antibiotics may lead to adverse events, multidrug resistant organism, and increased health care costs (12). Therefore, prophylactic antibiotic should only be provided if beneficial, and studies performed in the paediatric population assessing antibiotic prophylactic for PEG procedures are warranted to support recommendations in paediatric guidelines. To resolve this issue, we planned a prospective, randomised, double blind, multicenter trial to evaluate if a single i.v. dose of co-amoxiclav before PEG can reduce the incidence of peristomal wound and systemic infection in children.

Methods

Study design

This was a multicenter, randomized, double-blind, placebo-controlled study conducted in three Italian tertiary referral Centre for paediatric gastrointestinal endoscopy from April 2014 to April 2019. The study design was defined according to the international recognized guidelines for clinical studies (www.clinicaltrials.gov, Identifier NCT 01870167) and was approved by the local ethics committee (11/04/2013; prot. N°43513; rif. 2764). Written assent from young patients and informed consent from the legal guardian and patients aged >14 years were obtained.

Patients and methods

Eligible participants were all children aged 0 to 18 years referred for PEG placement to the paediatric gastroenterology units of Sapienza University of Rome, University of Messina and to the paediatric surgery unit of the "Papa Giovanni XXIII" Bergamo Hospital. Exclusion criteria were (1) contraindications for PEG, (2) ongoing antibiotic treatment, (3) antibiotic use within the past 4 days, (4) illness too severe to allow the patients to participate (i.e. neutropenia, acute renal failure) (5) allergy to any of the antibiotic alternatives.

Patients were randomized to receive a single i.v. dose of co-amoxiclav (50 mg/Kg) (or 75 mg/Kg ceftriaxone if penicillin allergic), or identically appearing saline solution about 30 minutes before the procedure. Randomization was performed using a permuted block design, with separate sequences of random numbers for each centre, to assign patients in roughly equal numbers to antibiotics or placebo group. The endoscopy nurse prepared the medication and the syringe out of sight of the study investigator and patients, and covered the syringe with an opaque sleeve so that study investigators were 'blinded'.

The antibiotic regimes used were selected on the basis of previous evidence according to the BSG guidelines (7,8). A standard endoscopic pull through technique was used to insert the PEG, with sterile technique used during insertion of introductory catheter via anterior abdominal wall and the external bolster of the PEG sited slightly away from the abdominal wall to avoid pressure necrosis (1). Twenty-four hours after PEG placement, water was administered through the tube and after 36 hours enteral feeding was started.

The following baseline data were collected: age, sex, indication for PEG, underlying disease. PEG sites were cleaned daily and bandaged dry without antiseptic ointment for 3 days by nursing staff. Blood samples were collected for measurement of haemoglobin, highly sensitive C reactive protein, white blood cells the day before and on day 3 and 14. The same blood samples and a sample for microscopic evaluation and bacterial or fungal culture were collected in patients with fever or other symptoms of local or systemic infection.

PEG site and symptoms, such as abdominal pain and fever were evaluated and treated accordingly 24 hours after PEG placement and on days 3, 7 and 14, by an observer blinded to the treatment group.

The PEG site appearance was scored according to the scoring system developed by Jain et al (13); where erythema around the site was scored as 0 = none, 1 = < 5 mm, 2 = 6–10 mm, 3 = 11–15 mm, 4 = > 15 mm; induration as 0 = none, 1 < 10 mm, 2 = 11–20 mm, 3 = > 20 mm and exudate as 0 = none, 1 = small serous, 2 = moderate serous, 3 = large serous ± sanguineous, 4 = purulent. When the maximum combined score was 8 or more, or a purulent exudate was noted the patient was considered to have developed a peristomal infection.

Study end points

The primary end point was the occurrence of a clinically identifiable wound infection, defined as presence of pus or a score of 8 or more, with or without microbiological evidence of bacterial or fungal infection from PEG site swabs. Secondary end point was the occurrence of systemic infection, defined as persistent fever (temperature >38.0 °C for >24 h) or clinical,

laboratory and microbiological evidence of invasive sepsis, and it was treated with systemic antibiotics

Sample size and statistical analysis

The sample size was calculated based on results from previous studies that reported an infection rate in control groups of approximately 35%, which might decrease to 14% using antibiotics (6). From this it was calculated that 20 patients per treatment arm would have been sufficient to detect this difference with a significance level of α-0.05 (two-sided) and a power of 80%. All data were analyzed using Statistical Package for MATLAB 2013a or Microsoft Excel (Office 2018). Description of mean ± standard deviation (SD), median with interquartile range (25%-75%), simple frequencies (n), proportions (or percentages) and rates of the given data on each variable has been calculated. Results were analysed using the Mann–Whitney test for continuous parameters and Fisher exact test (or chi-square test) to test group differences of proportions. Weight-for-age z-score was calculated as (observed value - median value of the reference population)/standard deviation value of reference population. A statistical significance level of two-tailed $P < 0.05$ was used.

We analysed the results primarily on a per protocol basis because a substantial number of patients

were given additional antibiotics for systemic infections. These patients were excluded from the principal analysis as it was felt they could influence the primary outcome measure of peristomal infection.

However, this scenario is common in clinical practice and it was felt important to reflect this by also performing an intention-to-treat analysis, which included these patients.

Results

The study flow is shown in Figure 1. During the study period, 106 patients with a need for PEG were considered for inclusion. Of these patients, 57 declined to participate in the study. The main reasons for parent's refusal to take part in the study were: nineteen parents didn't want to specify the causes of their refuse, 35 parents admitted that they were already troubled by the underlying disease of their child and the possible complications of PEG procedure, therefore they felt that participating in the study was an unnecessary additional stressful event, finally 3 parents refused the study for previous bad research experience.

The remaining 49 patients were randomly assigned to a study arm and were included in the intention to treat analysis: 24 patients in the antibiotic group [12 females and 12 males, median age of 52 months (IQR, 19-97)] and 25 patients in the placebo group [12 female and 13 males, median age of 40 months (IQR, 35-66)]. All patients of the antibiotic group received co-amoxiclav because none of them was allergic to penicillin.

One patient in the antibiotic group did not undergo PEG for anatomical reasons. Between PEG placement and follow-up visit one patient of the antibiotic group was lost to follow-up. Eight patients were given additional antibiotics for systemic infections during the follow-up period: 2 on antibiotics and 6 on placebo. These children were excluded from the per protocol

analysis of the primary outcome as they could influence the peristomal infection rate. The remaining 39 patients were analysed; 20 in the antibiotic group and 19 in the placebo group.

Baseline demographic and clinical characteristics of the 49 included patients are presented in Table 1. No substantial differences were found between the two groups regarding age, underlying disease and indications for PEG. The duration of hospital stay was significantly longer in the placebo group as compared to the antibiotic group (4.4±1.6 vs 3.5±1.05; p =0.02).

Peristomal infection

In the per protocol analysis, the occurrence of wound infection was 5 % (1/20) in the antibiotic group and 21% (4/19) in the placebo group [p= 0.13, 16% difference in proportions, OR 0.19, 95% CI 0.02-1.9].

In the intention to treat analysis, the occurrence of wound infection was 13 % (3/23) in the antibiotic group and 28 % (7/25) in the placebo group [p=0.2, 15 % difference in proportions, OR 0.4, 95% CI 0.9-1.7%].

All cases of isolated peristomal infection responded to treatment with topical disinfectant and/or antibiotics. All patients with systemic infection were successfully treated with iv. co-amoxiclav (50 mg/Kg) until the resolution of clinical and laboratory finding. There were no cases of cellulitis or necrotizing fasciitis.

Systemic infection

In the per protocol analysis of the secondary outcome (systemic infection rate) we have included also the eight patients which took an antibiotic course to treat systemic infection in the follow-up period, as they could not influence the systemic infection rate. The occurrence of systemic infection was 9% (2/22) in the antibiotic group and 27.2% (6/25) in the placebo group [p=0.17, 18% difference in proportions, OR 0.32, 95% CI 0.06-1.80%].

In the intention to treat analysis the occurrence of systemic infection was 8.7% (2/23) in the antibiotic group and 24% (6/25) in the placebo group [p=0.15, 15% difference in proportions, OR 0.3, 95% CI 0.05-1.7%]. All patients with systemic infection were successfully treated with iv. co-co-amoxiclav (50 mg/Kg) until the resolution of clinical and laboratory finding.

Complications

Table 2 summarises the complications rate in the two treatment groups after insertion of the PEG catheters. The overall infection rate was significantly higher in the placebo group as compared to the antibiotic group (40% vs 13,6%; p =0.04). None of the other complications was significantly over-represented in any of the two groups (table 2). No adverse reactions to the antibiotics used were recorded among the included patients.

Discussion

To the best of our knowledge this is the first randomized double blind controlled trial performed in children undergoing PEG procedures with and without antibiotic prophylaxis. It shows that a preoperative single dose of co-amoxiclav intravenous did not prevent peristomal

and systemic infections in the following two weeks. However, the overall infection rate and the duration of hospital admittance were significantly higher in the placebo group.

In contrast with the meta-analysis and the Cochrane review describing successful prophylactic antibiotic use in adults undergoing PEG placement (7,8), five retrospective paediatric studies found no significant differences in occurrence of infections between patients with and without antibiotic prophylaxis (9,10,14-16). An explanation for these different results may be the different population characteristics; indeed, neurological disorders are the main indication for PEG placement in children, whereas malignancies (mainly head and neck malignancies) and diabetes mellitus are the main indication in adults making this population more prone to infection (1-3,7). Without additional risk factors such as ventriculo-peritoneal shunt, congenital heart diseases or peritoneal dialysis children usually are in a better clinical condition than adult patients needing a PEG.

However, studies on complications and outcome of PEG in different groups of paediatric patients without those clear risk factors, however, led to controversial recommendations.

In a very recent retrospective study including 297 children undergoing PEG placement, prophylactic antibiotic therapy did not reduce the occurrence of wound infection but it showed to be beneficial with regards to fever, stoma leakage and duration of hospital stay (14). Engelmann et al., in another retrospective study demonstrated that the incidence of PEG-related local or systemic infections after PEG-placement was not significantly different between children with and without antibiotic prophylaxis, but the latter had a significantly higher mean body temperature as a marker of putative bacteraemia after the PEG procedure. The authors conclude suggesting the use of antibiotic prophylaxis in all paediatric patients regardless of the presence of risk factors after PEG placement until RCT on children with PEG will be published (10).

There are only two prospective observational studies including pediatric and adult patients with a wide range of years that didn't find any significant difference in infection rate between patients receiving and not receiving ABT. In a multivariate analysis, Fascetti-Leon et al even found that antibiotic prophylaxis was an independent risk factor for complications (2).

Our study confirms that a preoperative single dose of co-amoxiclav does not prevent peristomal and systemic infections. Noteworthy, in our study the overall infection rate and hospital length of stay were shorter in patients receiving co-amoxiclav than in the placebo group, and this is an important advantage in terms of both, saving resources and reducing the hospital-acquired infections which can also be increased by the length of hospitalization.

Alternatively, the approach of oral and/or topical antisepsis agents would, if proven to be beneficial, be an attractive alternative to antibiotic prophylaxis, which runs the risk of increasing bacterial resistance and antibiotic associated complications such as C. difficile related diarrhoea. Most peristomal infections are minor and readily respond to topical treatment or antibiotics, but occasionally more severe infection can occur. Although only two patients presented this complication, and all responded to treatment and fully recovered, it does have potentially serious implications. These factors need to be weighed up when

considering the overall benefits of antibiotic prophylaxis in this context, and a study of oral and/or topical antisepsis agents as an alternative is needed for these reasons.

Regarding the choice of the antibiotic used for prophylaxis there are some differences in the antibiotic prophylaxis recommendations given from the different societies. Different prophylactic antibiotic strategies have been tested but there is still disagreement regarding the type, dose and duration of antibiotic prophylaxis (17-19). We decided to follow recommendations from the BSG society, which, however, does not currently distinguish between malignant and non-malignant indications for PEG insertion. Therefore, we chose to use the co-amoxiclav instead of ceftriaxone also according to a recent RCT in adults, which showed that a single dose of intravenously co-amoxiclav reduced both percutaneous endoscopic gastrostomy site and systemic infections in patients without malignant disease. The other adult studies had heterogenous patient group including those with malignant diseases, an uncommon situation in children associated with a higher rate of infection at the insertion site (20). We believe that studies in which cerebrovascular disease and chronic neurological disease are the common reasons for PEG insertion are probably more relevant to hospital practice especially in children. Indeed, these were the main indication for PEG placement in our study.

Main limitations of the study are the small sample of patients despite responding adequately to the calculated sample size and the exclusion of patients at high risk of infection. Our result could be influenced by the exclusion of these patients at higher risk to develop infections (i.e. oncological and immunodeficient); and to the single dose antibiotic prophylaxis which could underestimate the preventive effect of co-amoxiclav in this context reducing the significance of our data. The duration of antibiotic prophylaxis may be one of the significant factors in determining risk of infection and this warrants further investigation. However, in a previous pediatric study no differences were found regarding infection rate comparing a single dose intravenous ceftriaxone to dual (intravenous ceftriaxone and metronidazole) 48-hour prophylactic antibiotic therapy in 32 consecutively allocated children undergoing a PEG procedure (21). Despite early feeding (even at 4 hrs after the procedure) has been shown to be safe and be associated with shorter hospital stay (22), in our study design the initiation of enteral feeding was delayed for 36 hrs after PEG placement according to the our clinical practice; nevertheless we believe that this fact didn't influence main study outcomes because the same timing was applied to all patients in both study groups.

Moreover, we don't have the data on the microscopic evaluation and bacterial or fungal culture of the patients that presented peristomal and systemic infection, therefore we don't know which microorganism was responsible for the infection. It has been assumed that the PEG is contaminated by pathogens as it is pulled through the oropharynx during insertion, an assumption supported by the fact that S. aureus is the most common organism found in peristomal infection. Because of this it has been suggested that antimicrobial chemoprophylaxis should be specifically aimed at oropharyngeal bacteria, such as S. aureus and Streptococcus spp., using cephalosporins or penicillin (23). However recent adult studies (4,17) highlight that there is a very high percentage of the patients with peristomal infection from methicillin-resistant Staphylococcus aureus (MRSA) and it has been suggested that

recommended antibiotic prophylactic regimens of cephalosporins or penicillins are likely to have reduced efficacy in centres where there is significant MRSA rates. In these circumstances an alternative approach would be to screen for MRSA and perform subsequent peristomal antisepsis following PEG insertion for those with MRSA colonization. Strength of this study includes the prospective, multicenter, double-blind randomized design and the use of objective markers of inflammations as well as the choice to use an established system to define peristomal infection, in order to maintain consistency between studies. This study is in accordance with some previous retrospective studies and it can reinforce the need of adequate preoperative antibiotic administration, however further studies should clarify the best treatment option in term of duration and population characteristics.

In conclusion, this multicentric RCT indicates that antibiotic prophylaxis with preoperative single dose of co-amoxiclav reduce the overall infection rate and the duration of hospital stay and suggest that it should be recommended in every children undergoing PEG placement.

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Figure and table legends

Figure 1: Flowchart of patients considered for the trial of antibiotic prophylaxis in patients with need for percutaneous endoscopic gastrostomy (PEG).

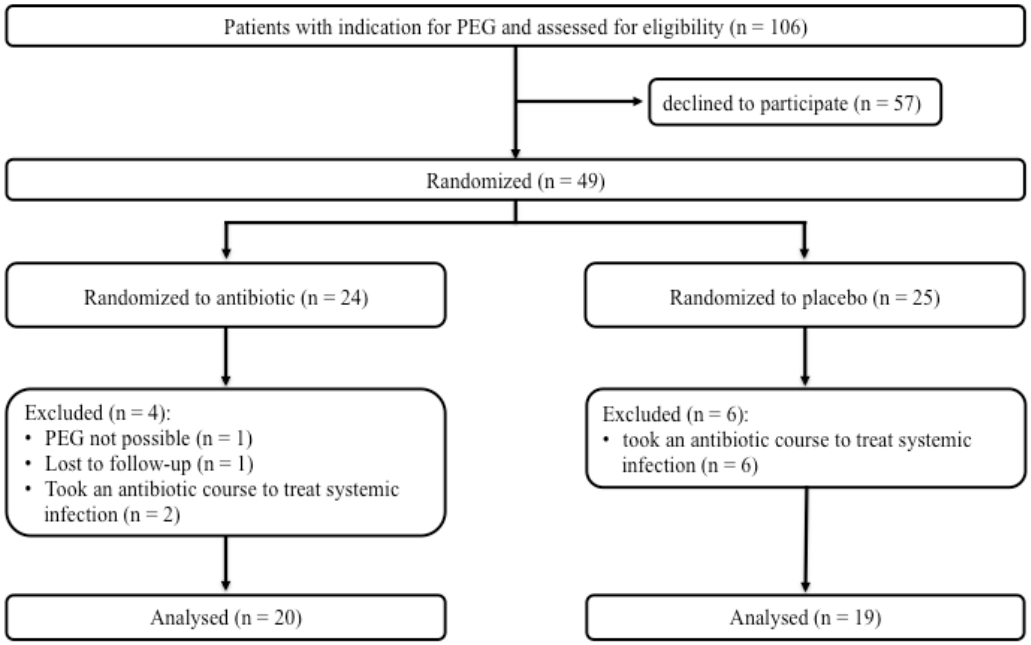

Table 1. Demographic and baseline characteristic of the study groups.

Variable	Antibiotic (n=24)	Placebo (n=25)	p-value
Sex, n (%)			
Female	12 (50)	12 (48)	0.889
Mean age (months)	52 (19-97)	40 (35-66)	0.168
Mean body weight (Kg)	11 (7-19)	15 (10-17)	0.909
Weight-for-age (z-score)	-0.01 (-0.1-0.75)	-0.5 (-1.3-0.03)	0.552
Underlying disease, n (%)			
• hypoxic ischemic encephalopathy	13 (54.3)	18 (72)	0.203
• malformative encephalopathy			
• intestinal pseudo-obstruction	6 (25)	2 (8)	0.111
• genetic syndrome	1 (4)	0 (0)	0.317
• prematurity	2 (8.3)	3 (12)	0.672
	2 (8.3)	0 (0)	0.145
Indication for PEG, n (%)			
• feeding problems	11 (46)	13 (52)	0.678
• malnutrition	12 (50)	9 (36)	0.327
• fluid administration	1 (4)	3 (12)	0.309

Continuous variables are expressed as arithmetic means ± SD or median (interquartile range).

Table 2. Outcomes and complications after insertion of the PEG catheter

Variable	**Antibiotic (n=24)**	**Placebo (n=25)**	**p-value**
Peristomal infection	3 (13)	7 (28)	0.199
Systemic infection	2 (8.7)	6 (24)	0.153
Overall infections	3 (13.6)	10 (40)	0.039
Duration of hospital admittance	3.5 ± 1.05	4.4 ± 1.6	0.018
Abdominal pain	2 (8)	3 (12.5)	0.608
Leakage around the catheter	3 (12)	4 (16.6)	0.649
Overgranulation	5 (20)	6 (25)	0.679
PEG procedure failed	1 (4)	0 (0)	0.317
No complications	14 (56)	13 (54)	0.889

Continuous variables are expressed as arithmetic means ± SD or median (interquartile range).