Format for ANSWERING REVIEWERS

January 28th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Manuscript NO 6619-review).

Title: Percutaneous Endoscopic Gastrostomy (PEG): Indications, Technique, Complications and Management.

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We wish to thank the reviewers for taking the time to go through our manuscript and make suggestions. We have made significant revisions to our manuscript and have improved it on the basis of these suggestions, as can be seen below:

Reviewer No 1:

- There needs to be careful attention to sentence construction and formatting. There are numerous examples where the determiners or prepositions are missing or incorrect. It is difficult to point all of these out given there are no lines given in the manuscript, but examples include page 1 in last sentence of the first paragraph "Tube feeding through gastrointestinal (GI) tract is considered when patients"; page 1 after reference [11] "The decision for placing tube should"… "not necessarily correlated with patient's nutritional improvement"; on page 2 after reference [15] "Some experts recommend that in patients who are not able to meet their nutritional need should start nasogastric"; page 5 under the section HIV/AIDS "In another study in children with AIDS who fed chronically by gastrostomy tube"; page 6 in the last sentence "In a systematic review of ten eligible randomized controlled trials (RCTs) that evaluated prophylactic antimicrobials in 1100 patients found a statistically"; page 8 under the section Metastasis of Malignancy to the stoma, "The diagnosis usually delayed until metastasis gets big enough to be visible or cause local presentation like or bleeding or infection", to highlight a few samples. There are many more throughout the text which require editing.
There are also several formatting errors on each page, in particular when referencing. Examples include page 1 in the first paragraph "bacteremia [3].", page 1 second last paragraph "nutritional response to PEG.[11]", page 4 "patients with high(>50%) and low (<50%) forced vital capacity(FVC) [21] … with ALS who had low FVC (< 50%)[22]." to mention a few. There are double spaces between some words in the middle of sentences and sometimes no space after full stops throughout the manuscript that should be edited.

Answer: The Sentences' constructional and formatting points well taken and corrected through out the manuscript.

- The take home message for the Gastroenterologist would be main indications, relative and absolute contraindications and main complications. A small discussion about blocked PEGs (see under page 9 comments) and truly dislodged PEGs would be helpful, as this is often not managed well in the outpatient setting.

Answer: Blocked vs. dislodged PEG tube: Based on the reviewer's comment, blockage of the tube described separately in " Post insertion care section" and tube dislodgment discussed under a new topic in " Complication section ".

- Page3/ comment 1: In the introduction it states that "the primary indication for enteral and parenteral feeding is the provision of nutritional support to meet metabolic requirements for patients suffering from temporary or permanent dysphagia" .This is misleading as enteral and parenteral feeding is not just indicated in patients with "temporary or permanent dysphagia", but a broad range of conditions. Suggest revise.

Answer: The reviewer's point well taken and the sentence changed to "…. provision of nutritional support to meet metabolic requirements for patients with inadequate oral intake ".

- Page 3/ comment 2: The end of the first paragraph states "Tube feeding through gastrointestinal (GI) tract is considered when patient cannot or will not swallow". Again, this is misleading as the "cannot or will not swallow" is not the only indication for tube feeding, and in general, the majority of indications for tube feeding in hospitals would be used for insufficient oral intake not necessarily in patients who cannot or will not swallow. Furthermore, a PEG or tube feeding is not indicated just because a patient will not swallow.

Answer: The sentence changed to " Tube feeding through the gastrointestinal (GI) tract is mainly considered in patients with insufficient oral intake who have functional GI system and … ".

- Page 3/ comment 3: In the second last paragraph of the page after reference [11], the authors mention "it is difficult to access improvement of functional response to PEG". Access is not the right word in this context – suggest revise.

Answer: The word " access " was a typo and the correct word was " assess ". This sentence removed during the revision.

- Page 4/ comment 1: In the second line there is unnecessary repetition: "the mean loss of body weight in all patients during the three months was 1.35 +/- 1.5 kg in the three months before starting PEG tube nutrition" - suggest remove

Answer: The sentence changed to " In a 4 year prospective study of 210 patients (with both malignant and benign underlying diseases) the mean weight loss in the three-month period before starting PEG tube nutrition was 11.35 +/- 1.5 kg, while the mean weight gain at the end of the 12-month feeding via PEG tube was 3.5 +/- 1.7 kg ".

- Page 4/ comment 2: In line 4 “suggests that initiation of PEG tube nutrition as soon as medical necessity is established to prevent further significant weight loss” – suggest change “to” to “can”

Answer: The sentence changed to “ This finding suggests that initiation of PEG tube nutrition, as soon as medical necessity is established, can prevent further significant weight loss ”.

- Page 4/ comment 3: Under the heading “ALS”, the second line mentions “anatomic deformation”. Deformity is perhaps a better choice of word

Answer: The sentence changed to “ In some patients the technique of PEG tube placement should be modified in a view of associated anatomic deformity ”.

- Page 4/ comment 4: Line 6 under the “ALS” paragraph states “non-invasive ventilations”. Ventilation is singular.

Answer: The sentence changed to “ … PEG can be done in these patients under procedural non-invasive ventilation (NIV) with minimal peri- and post-procedural complications ”.

- Page 4/ comment 5: One of the major issues and discussions that must be raised with PEG insertion is the Ethical and moral dilemma that is associated with PEG insertion. It is very easy to just insert a PEG in anyone, but a careful discussion must be had, particularly in patients with neurological dysphagia where there is no prospect for recovery (dementia, large stroke, persistent vegetative states). This warrants a mention, as it is often the most difficult aspect of PEG insertion.

Answer: Based on the reviewer’s comment, this issue discussed in “ Preparation” section as following “ Informed consent should be obtained from patients or their legal surrogate decision makers. A considerable number of the patients undergoing PEG tube placement don’t have required capacity to give informed consent, due to advanced dementia or other underlying medical conditions impairing their cognitive function (stroke, advanced cancer, failure of other internal organs). Obtaining consent from this population can become complicated. Several studies suggest that quality of informed consent in patients undergoing PEGs is inadequate [131, 132]. The intent of informed consent is aimed to enhance the patient’s care by giving the patient complete information on the benefits and burdens of tube feeding before PEG insertion”.

- Page 4/ comment 6: Neurological disorders should be expanded to include cerebral palsy and bulbar palsies.

Answer: The subheading “ALS ” changed to “Motor neuron disease/ ALS ” and the following paragraph added “ The role of PEG tube also has been described in nutritional support of other motor neuron and dysfunctional motor diseases like cerebral palsy and bulbar palsy [23-25]. These patients

frequently have feeding and swallowing problems that may lead to poor nutritional status, growth failure, chronic pulmonary aspiration and infection. The epidemiologic oxford feeding study reported significant correlation between the severity of motor impairments and need for gastrostomy feeding [26] ".

- Page 5/ comment 1: In line two the first word of the second sentence is not capitalised and should be.

Answer: The sentence changes as " In a recent study to assess effect…. ".

- Page 5/ comment 2: Cancer and gastric decompression appear as subheadings. When looking at page 4, the overall heading under which these fall is "Neurological and psychomotor retardation". Cancer and gastric decompression do not fall under the Neurological and psychomotor retardation heading and should be removed from this part and perhaps would be better under the "Miscellaneous" heading. I do not think these two heading are really required.

Answer: The mentioned two topics moved into " Miscellaneous " section.

- Page 5/ comment 3: Under the heading "Cancer", where the authors mention "some degrees", degree should be singular.

The sentence changes to "…. malignancy have some degree of malnutrition ".

- Page 5/ Comment 4: Under "Reduced level of consciousness" in the fourth line, "physical function of GI system restores", restores should be restored.

Answer: The sentence changed to " Generally in order to prevent nutrition depletion, enteral feeding should be started as early as physiological function of the GI system restored ".

- Page 5/ comment 5: It is now rare to need to insert a PEG with "HIV/AIDS" or "Cystic fibrosis" given that these patients have a normally functioning gut. Dedicated paragraphs are probably not required, and it perhaps may be best to discuss in one paragraph under miscellaneous.

Answer: The two topics " HIV/AIDS " and " Cystic fibrosis " moved under the section of " Miscellaneous".

- Page 5/ comment 6: Under the section “Cystic Fibrosis” “good nutrition status” should be “nutritional status”.

Answer: The sentence changed to “ In patients with cystic fibrosis, the better nutritional status is associated with superior survival “.

- Page 5/ comment 7: In Crohn’s disease, it is now uncommon to need to insert a PEG for enteral feeding with the large range of oral nutritional elemental supplements currently available, and would be reserved only in patients who don’t tolerate oral elemental diets. There would also be a concern inserted PEGs in those with upper GI Crohn’s as the PEG tract can become involved. Again, I would include a short sentence about this in a miscellaneous paragraph, as currently it appears that this is a common indication. The other possibility would be to divide the indications into mechanical dysphagia (head and neck cancer), neurological dysphagia (stroke, ALS, dementia, etc.), failure to meet nutritional requirements due to malabsorption (HIV/AIDS, Cystic Fibrosis, Crohn’s, renal failure etc.…).

Answer: The paragraph edited based on the reviewer’s comment and the following sentence added “ However, considering the large number of oral nutritional supplements and other nutritional alternatives available, nowadays it is uncommon to insert PEG tube for enteral feeding “.

- Page 6/ comment 1: In the first line “overtime” should be “over time”

Answer: The sentence changed to “… but overtime its safety in usage … “.

- Page 6/ comment 2: Box 3” appears before Box 2 and these box headings should be changed according to first appearance in the manuscript.

A**nswer: Tables sequence changes based on the reviewer’s comment.**

- Page 6/ comment 3: The section “Special Considerations and contraindications”:
I think this paragraph is better divided into two sections as these describe totally different clinical scenarios. I would keep special considerations (and perhaps put Dementia, global neurological dysphagia with little prospect for recovery in this section). I would then have a contraindication section and divide this into relative contraindications and absolute contraindications.

Answer: The PEG tube contraindications divided into absolute and relative contraindication as recommended “ Some of the absolute contraindications of PEG tube placement are summarized in Table 2. Besides these absolute contraindications conditions like the presence of non-obstructing

oropharyngeal or esophageal malignancy, hepatomegaly, splenomegaly, peritoneal dialysis, portal hypertension with gastric varices and history of previous partial gastrectomy are considered as relative contraindications ". Also " special considerations " mentioned as a separate subheading in " contraindications " section.

- Page 6/ comment 4 a: Box 2 should be Box 3.There is a comprehensive list in this box that is not discussed in the main text of the article, some of which are very important. Suggest including the important ones in the main body of the text.

Answer: Tables sequence changes based on the reviewer's comment and tube dislodgment, tube blockage and granuloma formation discussed through out the manuscript in " complication " and " post insertion care" sections.

- Page 6/ comment 4 b: In the first paragraph, the authors state "there is no procedure-related mortality". Although some recent studies have quoted 0% procedure-related mortality, these have been in small centres, and given PEG insertion is an invasive procedure and this is potentially an unwell group of patient, I don't think you can say that there is "no procedure-related mortality". There are multiple studies that have shown procedure related mortality of around 2% (J Sheehan IMJ 2013, M Hull Lancet 1993, R Zera Surgical Endoscopy 1993). This includes the American Gastroenterological Society position statement on PEG insertion where a procedure-related mortality of 1-3% was quoted. More recently, figures in the order of 0.17-2% have been quoted. It would be better to say that the procedure-related mortality is low.

Answer: The sentence changed to "Although there is a low procedure-related mortality ..." based on reviewer's comment.

- Page 6/ comment 4 c: With complications, most clinicians are interested in the severe or significant complications, so I would recommend listing these first, or dividing it into common and uncommon complications (especially since ~20% will develop minor complications).

Answer: Major complication discussed first as recommended.

- Page 6/ comment 4 d: Under "Local wound infection" the first word of the first sentence is in bold and should not be.

The sentence changed to " The tube site infection is the most common ...".

- Page 8/ comment 1: Under “Internal organ injury” the authors merely mention “Iatrogenic perforation”. During PEG insertion perforation of stomach is deliberate. This should be clarified.

Answer: The paragraph changed as following based on the reviewer’s comment “Any intra- abdominal organ, more likely colon [76] and small bowel [77] and rarely liver [78] and spleen [69], is at risk of injury during PEG tube placement. Also few cases of complete laceration of the stomach following tube insertion have been reported in the literature [79]. Iatrogenic perforation of the bowels during PEG insertion is more common among patients in their extreme ages due to laxity of the colonic mesentery [80]. Patients with bowel injury may develop the classic signs of peritoneal irritation. However in some instances, the diagnosis is challenging since candidates for PEG tube nutrition are not always easily communicable due to their underlying altered mental statues. In addition, the persistence of transient subclinical pneumoperitoneum occurs during PEG [85] limits the utility of plain films in diagnosis of suspected visceral perforation. A watchful follow-up is important after any PEG tube insertion and there should be a low threshold for further investigation. Performing CT scan with water-soluble contrast, or incase of hemodynamic instability fluoroscopy, is a useful alternative to confirm GI integrity in this setting. Any evidence of active leakage of contrast into the peritoneal cavity in the presence of the signs of peritonitis warrants for emergent surgical intervention ”.

- Page 8/ comment 2: Under “metastasis of malignancy to the stoma”. Perhaps “Tumour seeding of the stoma” may better describe this.

Answer: Subheading changed to “ Tumor seeding of the stoma ” based on the reviewer’s comment.

- Page 9/ comment 1: In line 2, “peg” should be “PEG” to be consistent with the abbreviation and the remainder of the manuscript

Answer: The sentence changed to “ … undergoing PEG placement don’t have required mental capacity to give informed consent …”.

- Page 9/ comment 2: There is a section titled “techniques and after care”. I would separate the two clearly, as after care instructions are very important and currently they are buried in the procedural aspects of PEG insertion. Then it is confusing as the next section is “Post-insertion care”. Perhaps it would be better to combine the after care together. The authors mention the most commons ways of inserting a PEG (eg. Push, pull methods), however there is no mention of trans-illumination and finger indentation, which are keys ways of identifying ideal PEG placement.

Answer: After care and Post insertion care sections are combined under the title of “ Post-insertion care” based on the reviewer’s comment. Recommended technical points added to “ Insertion Technique “ section.

- Page 9/ comment 3: In the “Post-insertion care” section in paragraph 2, the Authors state “If dislodgement occurs attempt can be made to clear it by means of attaching a 50mL syringe filled with warm water to the tube”. Dislodgement means the tube is no longer in the position it was. Do the authors means blocked? Blocked PEG tubes should be addressed in this manuscript. I think true dislodgement of PEG tubes should be mentioned as this is a common cause of Emergency Department presentation in patients with PEGs.

Answer: Based on the reviewer’s comment, blockage of the tube described in “ Post insertion care section ” section and tube dislodgment discussed under a new topic in “ complication “ section.

- Page 9/ comment 4: Perhaps removal of PEG should be a separate section or a sub heading.

Answer: PEG removal is discussed under separate heading.

- Page 18-20/ comment 1: Box 3 should be box 2 and box 2 should be box 3 as mentioned above.

Answer: The reviewer’s comment well taken and Tables’ numbers edited.

- Page 18-20/ comment 2: There are formatting issues within the boxes (comma at the end of Facial surgery, failure to capitalize some words.

Answer: Formatting issues addressed in Tables.

Reviewer No 2:

- The manuscript should be submitted according to "Instruction to Authors", and the style for references should be modified according to the WJG guidelines.

Answer: The mentioned point well taken and manuscript edited through out based on instruction for authors' guideline.

- Page 3, last line. Box 1 should be removed and replaced by a discussion about the clinical settings in which PEG placement is controversial, such as advanced dementia, end-stage-AIDS, terminal cancer (see: Angus F. et al. The percutaneous endoscopic gastrostomy tube: medical and ethical issues in placament. Am J Gastroenterol 2003; 98: 272-277; DeLegge MH. et al. Ethical and medicolegal aspects of PEG-tube placement and …..Gastrointest Endosc 2005; 62: 952-959; Volkert D. et al. ESPEN Guidelines on enteral nutrition: geratrics. Clinical Nutrition 2006; 25: 330-360; Hwang D et al. Feeding tubes and health costs postinsertion in nursing home residents with advanced dementia. J Pain Symptom manage 2013).

Answer: Recommended controversial issues discussed separately under the section " Miscellaneous " and referenced appropriately based on the reviewer's comment.

- Page 5. After reference 34, the authors should add some comment on the increase in annual inpatient health care costs of PEG tube insertion in patients with advanced dementia (Hwang D et al. Feeding tubes and health costs post-insertion in nursing home residents with advanced dementia. J Pain Symptom manage 2013).

Answer: The following sentence and reference added based on the reviewer's comment " In one study, PEG tube insertion in nursing home residents with advanced dementia showed to be associated with significant increase in annual inpatient health care costs as well as in hospital and intensive care unit stay ".

- Page 6, complications, line 6. Please, add the following reference: Zopf Y et al. Predictive factors of mortality after PEG insertion: guidance for clinical practice. JPEN 2011; 35: 50-55.

Answer: Recommended reference added to support the text.

- Page 8, Buried bumper syndrome. At the end (.. or external traction of the tube [112-113]), the authors should add "It can be avoided by adequate aftercare treatment" or similar sentence.

Answer: The following sentence added based on reviewer's comment " This complication can be easily avoided by regular checking of the PEG tube position, leaving a small distance between the external bumper and the resident's skin and daily 180-360 degree rotation of the tube".

- Page 9, Preparation. At the end of the last sentence (The current gold standard is 2 g cephazolin iv) some reference should be added.

Answer: Recommended reference added to support the text.

Reviewer No 3:

- An abstract is too short.

Answer: Abstract edited based on reviewer's comment.

- There is almost no description of one-step low profile button technique.

Answer: The following paragraph added to " Insertion Technique " section to describe low profile button PEG tube based on reviewer's comment. " Long-term protruding gastrostomy tubes may not be favorable in some patients due to risk of periostomal leakage, inadvertent catheter dislodgment and cosmetic issues. These regular tubes can be replaced by a skin level low profile button gastrostomy tube after maturation of stoma canal upon selected patient's request [128-130]. Their higher expenses and replacement need every 6 months limits their routine use and they are often reserved for adolescent patients for cosmetic reasons. Although one-step button gastrostomy tube insertion can be done similar to the routine "pull technique" PEG tube placement, generally it is recommended to wait until complete maturation of the stoma [131] ".

- In the part of complications the authors should mention granulation tissue as the most frequent complication after PEG insertion.

Answer: The following paragraph added to " complication " section to describe " granuloma formation" as one of the common PEG tube complication. " Granuloma formation: The development of hyper-granulation tissue around the gastrostomy tube is one of the common complications observed in patients with PEG tube [68, 69]. Although the exact mechanism of granuloma formation has not been recognized, factors like friction from a poorly secured tube and excess moisture from fluid leakage causing skin breakdown at the exit site seems to be responsible [68, 70]. The presence of granuloma itself is not a life threatening complication, but it's moist and highly vascularized surface prone the patients to wound infection, biofilm formation and bleeding. While wide variety of treatment options from application of topical antimicrobial agents and low dose steroids to cauterization by silver nitrate and surgical removal has been described in the literature, none proved to be more effective than others [68, 71]. "

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,

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