Author's response to reviews

Title: Fully covered self-expandable metal stents (SEMS), partially covered SEMS and self-expandable plastic stents for the treatment of benign esophageal ruptures and anastomotic leaks

Authors:

Petra GA van Boeckel (p.g.a.vanboeckel@umcutrecht.nl)
Kulwinder S Dua (kdua@mcw.edu)
Bas LAM Weusten (b.weusten@antoniusziekenhuis.nl)
Ruben JH Schmits (ruben.schmits@planet.nl)
Naveen Surapaneni (nsurapaneni@mcw.edu)
Robin Timmer (r.timmer@antoniusziekenhuis.nl)
Frank P Vleggaar (f.vleggaar@umcutrecht.nl)
Peter D Siersema (p.d.siersema@umcutrecht.nl)

Version: 3 Date: 12 January 2012

Author's response to reviews: see over
Dear Dr. B. Wijnhoven,

Thank you for reviewing our manuscript, entitled:

MS: 1653074273581524
Fully covered self-expandable metal stents (SEMS), partially covered SEMS and self-expandable plastic stents for the treatment of benign esophageal ruptures and anastomotic leaks

The reviews were very helpful in improving the quality of our paper. In the following, you can find our responses to the comments made by the reviewers:

Reviewer 1

Minor comments
1. Stents were placed for different indications, namely anastomotic leak, iatrogenic rupture, Boerhaave's syndrome and other causes. Were the different stents (equally) divided for the different indications or did the attending physician prefer one of these stents in a specific indication?

The attending physician did not prefer one of these stents for a specific indication. The chosen stent type depended on the availability of that type at the moment of stent placement.

2. How many days-months after stent removal were patients in follow up. What was the follow-up time?

Median follow-up was 470 days (range 25-1200 days). Please see, Results on page 6.

Reviewer 2

1. The study is well written, clear and concise. The authors are all from well-respected GI units. However, the inherent methodological problems with this study as well as many other case series are numerous: retrospective analysis
We are aware of the limitations of this study due to the retrospective design of the study as we already mentioned in the Discussion on page 10. However, the only true evidence will come from a randomized trial comparing these two treatment modalities in a well defined population. Nevertheless, the limited number of patients for such a trial and the promising results of stent placement make it difficult to perform such a trial.

- **three centers involved (2 from the Netherlands and one from the USA)**

We believe that the involvement of 3 centers did not affect our results. All three centers are very experienced in this area and treat patients with these disorders in the same way.

- **very different etiologies of esophageal injury-rupture**

It is already known that not the etiology of the esophageal injury-rupture but the time between occurrence of an esophageal rupture or leak and its actual treatment, either surgical or endoscopic, is probably the most critical prognostic factor. A longer delay between a rupture or leak and its treatment has been reported to be associated with a worsening of the prognosis due to septic complications from an infected fluid accumulation in the mediastinum or pleural cavity. We therefore think that the inclusion of different esophageal injury-rupture etiologies did not affect our results to a large extent.

- **timing between onset of injury and treatment-stent placement unknown**

We agree with the reviewer that the time between onset of rupture or leak and performing an intervention is the most critical prognostic factor with an increasing delay between rupture or leak and treatment being associated with an inferior prognosis due to higher occurrence of (septic) complications (please see also our previous reply). In our study, we noticed that the majority of patients (90%) presented more than 24 hours after the onset of rupture. Therefore, it was not possible to determine whether early presentation resulted in a better prognosis of patients.

- **no information on the number of patients with similar esophageal ruptures and leaks who did not undergo stent placement in the three centers during the study period (what is the denominator for the study period??) hence, highly selective indications for stent placement in these patients that remain obscure for the reader**

The guideline in all three centers was to place a stent in case of an esophageal rupture or leak during the study period. Only patients with larger ruptures or leaks (>70% of the circumference) underwent surgery and not stent placement. Unfortunately we were unable to track down this information in the participating centers.

- **comparison with surgical series impossible due to lack of information on grade, severity and extent of contamination, size of rupture, location of rupture etc. etc.**
The mortality rate associated with stent placement for this indication (13%) may well compare favorably to surgical management (12%-50%). There is currently no guideline which type of esophageal rupture or leak should be treated with stent placement or primary surgery. Stent placement has been proposed for ruptures or leaks less than 70% of the circumference, with surgery being reserved for larger ruptures or leaks (34). Doniec et al. recently reported a patient with a complete dehiscence that was also treated with stent placement, resulting in complete closure without a complicated course. We have a similar experience in a few patients (unpublished). Please see Discussion on page 9-10. We agree that the only true evidence will come from a RCT comparing these two treatment modalities, with special reference to the underlying disorder, extent and time since the rupture or leak occurred and severity of the extra-esophageal contamination. As stated before, the limited number of patients for such a trial and the promising results of stenting make such a trial difficult to perform.

2. The comparison of the efficacy of three different stent types is not valid. There were no differences between the three stent types but the indication and reasons to prefer one above the other in this series is unclear. Moreover the number of patients per group is small. Given the heterogeneous patient population and underlying disorders in the groups no comment or conclusion whatsoever can be made.

We respectfully disagree with the reviewer that there were no differences between the different stent types used. SEPS and FSEMS are both fully covered and have therefore a higher risk of stent migration. Reactive nonmalignant tissue in- or overgrowth is particularly causing problems when stents are inserted for a longer period, This has been reported to occur more commonly with PSEMS than with FSEMS or SEPS, because of the bare ends on either side of the stent. We do agree with the reviewer that the number of patients per group is small, but this is one of the largest series in the literature as can be seen in a recently published review (van Boeckel et al. Stent placement for benign ruptures or anastomotic leaks: a pooled analysis with special emphasis on stent type, Aliment Pharmacol Therap 2011). Please see also Comment 1, Reviewer 2.

3. The authors indeed make a valid comment on the importance of adequate drainage of sepsis at and around the site of oesophageal injury. This is the most important aspect of treatment of esophageal rupture and anastomotic leaks. The questions still remains if stent placement at all truly does aid or on the (spontaneous) healing of oesophageal leaks. Several surgical approaches with T-tube placement with surgical drainage or external drainage alone is succesful have been published. Does a stent truly favourably alter the course of the disease? That is the question that has not been answered so far. Therefore the efficacy of stent placement in healing benign esophageal leaks and perforations can not really be commented on.
Stents are found to be able to effectively seal esophageal leaks or ruptures and allow healing of the esophageal wall; however, and we fully agree with the reviewer, only when adequate concurrent drainage of fluid collections in the mediastinum or pleural cavity is performed. An advantage of stent placement is that patients can eat normally, which may have a positive effect on the healing process.

4. Can the authors comment on the time between onset of oesophageal trauma/rupture and stent placement? This is an important determinant of success with surgery as well as stent placement.

In our study, we were able to differentiate between stents placed less or more or more then 24 hours after the onset of rupture/leak. It was however impossible to find in the majority of cases the exact time between onset of esophageal trauma/rupture and stent placement. This is also caused by the fact that it anyhow remains difficult to determine the exact onset of an esophageal rupture or leak.

The same is true for the extent of collateral damage/contamination of the mediastinum-pleural cavity.

In 24 (46%) patients, concurrent drainage of the pleural cavity (n=12), mediastum (n=4) or both (n=8) was performed, This was either surgically (n=18 (75%)) or radiologically (n=6 (25%)) performed. Please see Results on page 6.

In line with other reports that stent placement in the acute setting directly after occurrence of oesophageal rupture is successful because of less contamination. E.g. 9 patients had a rupture after pneumatic dilatation that likely was diagnosed at the time of the endoscopic treatment. These patients likely benefited from a stent. Whereas the patients with Boerhaave syndrome (n=4) likely were diagnosed at a later stage (12-24 hrs??). Hence stent placement might have been less effective.

The reviewer is correct that one would expect that patients with an endoscopic cause of a perforation would have presented earlier than those with a traumatic origin. This was however not the case. Of all 9 patients with a rupture after pneumatic dilatation, “only” five (10%) had a stent placed within 24 hours, showing that some improvement is needed! Please see Table 1.

Can the authors give details on the success rate for the different underlying pathophysiology/diseases? This is crucial for interpretation of the results.

Clinical success for patients with an anastomotic leak was 69%, an iatrogenic rupture 54%, Boerhaave syndrome 100% and rupture of other etiology 33%. As mentioned above, we do not really believe that the heterogeneous population influenced our results. Please see, Comment 1, Reviewer 2.
The conclusion of the study that covered stents are effective and safe should be weakened and more in balance with the reported complications. The safety with two ruptures upon removal of the stent, two patients with bleeding including one stent related death should not be forgotten about. Furthermore, stent migration remains a big problem, as shown in this study. Lastly, one patient needed an operation to remove the stent.

Following the suggestion of the reviewer, we changed our conclusion to ‘Covered stent placement for a period of 6-8 weeks may be an alternative to surgery for treating benign esophageal ruptures and anastomotic leaks’ Please see Abstract on page 1 and Discussion 10.

6. The chosen (primary) endpoint of the study was sealing of rupture or leak confirmed by endoscopy. This can since the accuracy of endoscopy to determine complete sealing is by far not 100%. Ideally, a combination of an esophagogram/CT with oral contrast and endoscopy would probably have.

We fully agree with the reviewer that in an ideal study situation a combination of esophagogram/CT with oral contrast and endoscopy would be preferable, because of the retrospective design of this study we lack this information.

We hope that we satisfactorily replies to all questions/comments, however, we kindly ask you to contact us for any further information you may require.

Yours sincerely,
on behalf of the co-authors

P.G.A. van Boeckel, MD

Department of Gastroenterology and Hepatology
University Medical Center Utrecht, the Netherlands