

Novel insights in the pathophysiology of colorectal anastomotic leakage

Citation for published version (APA):

Jongen, A. C. H. M. (2019). *Novel insights in the pathophysiology of colorectal anastomotic leakage*. Maastricht University. <https://doi.org/10.26481/dis.20190926aj>

Document status and date:

Published: 01/01/2019

DOI:

[10.26481/dis.20190926aj](https://doi.org/10.26481/dis.20190926aj)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Valorisation

Valorisation

The societal and economic impact of scientific research has become increasingly important during the last decade. This chapter therefore focuses on the impact that the knowledge acquired from the different projects described in this thesis may have on the society and economy, and discusses the influence these results have on the current scientific focus in the field of colorectal anastomotic leakage.

Economical and societal impact

10,000 oncological colorectal resections are performed on a yearly basis in the Netherlands. Of these, 10% (1000 patients) will be complicated by colorectal anastomotic leakage (CAL). It is predicted that the incidence rates of colorectal carcinoma will increase substantially over the next decades due to the implementation of the national screening programme for colorectal cancer and the ageing population. This would also implicate a strong increase in patients suffering the consequences of CAL. Patients who develop CAL experience significant morbidity, and the mortality rates associated with the occurrence of CAL are also still high: around 15% of the patients who develop a leak will eventually die of the consequences. These numbers/percentages have remained equally high the last decades.

The occurrence of the complication after colorectal surgery causes a three- to fivefold increase in healthcare costs compared to a similar surgery with a normal postoperative course. The exact additional costs associated with CAL have not been intensively studied in the Netherlands, but American studies have calculated the extra financial burden associated with leakage per 1000 operated patients to lay around 25.7 million euros. These costs are mainly generated due to the prolonged hospital stay (7-10 days), the increased employment of diagnostic tests, reoperations, and/or when the patient is temporarily admitted to the intensive care unit. The costs that are indirectly involved with the complication are generated in rehabilitation, physiotherapy and prolonged absence from work.

The burden of the complication goes beyond its economical impact, as CAL is also associated with a substantial impact on the Health-Related Quality of Life (HRQoL) of our patients. It is believed that quality of life is affected by the same factors that cause the increase in costs associated with CAL (prolonged hospital stay, absence from work), but also by the need of the construction of a stoma. If a reoperation is needed when CAL occurs, the anastomosis is usually taken down and a permanent colostomy is

constructed. Studies have shown that these stomas (either temporary or permanent) severely affect patients' body image and quality of life and lead to depression and anxiety. Lastly, the occurrence of CAL has been associated with an impaired oncological outcome, leading to an increase in local recurrence and a decrease in disease-specific survival.

Reducing the incidence of CAL

We believe that it is possible to achieve a significant reduction in the incidence of leakage rates and the associated morbidity and mortality by a combination of several techniques. We feel that with the REVEAL study, that currently is still on-going in the MUMC+ in Maastricht, Zuyderland Medical Centre in Sittard-Geleen/Heerlen and in VieCuri Medical Centre in Veldhoven, an important step in the right direction can be made. We believe that a combination of patient-derived factors such as a compromised immune response, sarcopenia, genetic predisposition, an aberrant intestinal microbiome composition, and surgery-related factors such as surgical stress, ischemia and a derailed systemic response, are responsible for the occurrence of CAL. Based on data from our own previous studies, in which we found that certain plasma markers and genetic factors are predictive of the risk of CAL, the REVEAL study is set up to collect a large set of patient data and patient samples (plasma, exhaled air, faeces, buccal swabs, tissue). With these data and with the use of machine-learning models, we will be able to assess the risk of the development of CAL in every individual patient. Until now, it has been extremely difficult to predict which patient will leak following surgery; no specific lab test exists that gives an adequate indication for the risk, and also the findings during surgery (e.g. aspect of the bowel and the quality of the anastomosis) have been shown to be of insufficient predictive value for CAL. With the results of the REVEAL-study, we will be able to make an adequate estimation of the risk of CAL for every individual patient, even before they have been subjected to surgery. A clear risk classification – and the associated guidelines for each risk class - will ameliorate communication between clinicians and patients. Moreover, with these results, one can also identify the patients with low risk of leakage, possibly saving them from an unnecessary deviating stoma and the associated impact on their quality of life. With the results from the REVEAL-study, the decision to construct an anastomosis or to opt for a permanent colostomy in the frail patient will no longer be based on the 'gut feeling' of the surgeon, but supported by evidence from a large multicentre observational study. As we have passed the 80% inclusion of in total 558 patients, we expect to be able to present the first results shortly.

Beside the preoperative risk assessment, the REVEAL study has a second important goal: to shorten time to diagnosis of CAL following surgery. This would also lead to a decrease in mortality and health care costs, as research has shown that early diagnosis leads to improved outcome. Lastly, a combination of metabolic and microbial signatures derived from the REVEAL data, more insight is generated in the processes of colorectal anastomotic healing and leakage. This could also lead to the development of new preventive and treatment strategies, such as nutritional interventions or influencing the microbiome by anti- or probiotics etcetera - strategies that are desperately needed, as our current best preventive method of severe CAL is a deviating stoma.

New research has stressed the importance of the surgery itself as a period that can be influenced in order to improve outcome. We participated in the nationwide Leak Check study, which investigated several factors that can be improved during surgery. This study showed that high peri-operative glucose-levels, low preoperative haemoglobin levels, low body temperature are all modifiable risk factors that can be improved and possibly reduce the rates of leakage. Another important tool that can be used during surgery to aid the battle against CAL is the use of fluorescence imaging to assess the perfusion of the intestine at the future anastomotic site during surgery. This is in line with our own work on intestinal fatty acid binding protein (I-FABP), which is a marker for intestinal damage and shows a significant increase in case of intestinal hypoperfusion.

We believe that in order to further reduce the leakage rates, new and innovative techniques are needed to further reduce the incidence of CAL. In the general introduction of this thesis, we have elaborated on why increased insight in the healing processes of the intestine and the pathophysiology behind CAL is relevant for current and future research. Several studies presented in this thesis have aimed at gaining knowledge on certain pathways, and possible fields of interest for such preventive methods have been investigated. In combination with the results from the clinical study (REVEAL), we will be able to select patients that will benefit most from new therapies, hopefully reducing the risk of a leakage to acceptable levels.

Importance of collaboration

During the past four years, fruitful collaborations have been established with different research groups in the Netherlands and abroad. Our research group has been part of the Taskforce Colorectal Anastomotic leakage, which is a platform for clinicians and researchers in the Netherlands to exchange ideas on this topic. Collaboration on a national level allows for initiation of new projects in multiple centres simultaneously, of

which the Leak Check is a good example. The consensus survey and definition review (Chapter 2 and 3, respectively) have already showed what combined (international) forces could bring about. The final part of the quest to a generally accepted definition for CAL is currently being conducted across all continents in the form of a Delphi analysis. In this analysis, many renowned researchers are asked for their opinion and are given the opportunity to elaborate on their thoughts together, eventually coming to consensus about a certain topic. We are positive that the new definition to be presented soon will be adopted by researchers and clinicians worldwide.