Anastomotic leaks in gastrointestinal surgery and their prevention

ABSTRACT: Anastomotic leak in the gastrointestinal tract is one of the most important complications of resection. They are the main cause of reoperation, their occurrence worsens the prognosis of the patient, increasing the proportion of direct mortality, as well as being a significant risk factor for recurrence of cancer.

The risk of leaks within the gastrointestinal tract is greatly varied, depending on the location and extent of the resection, but also on patient, disease or a surgical procedure, including surgeon. To determine the potential risk of leakage can be significant for introduction some prophylactic actions. Some of them have the character of general recommendations, as proper nutrition of the patient in the perioperative period, while another part is directly connected to the surgical procedure. The second group includes protective stoma, the use of tissue glues, insertion transrectal drain for rectal anastomosis decompression, the use of stents or the use of collagen matrix coated with fibrinogen and thrombin.

Important to reduce the proportion of leaks can be more precise and targeted prophylactic recommendations, based on the individualized determination of risk factors leaks. Further research for this purpose are necessary for this purpose, the big hope can be associated with data obtained through mobile applications.

KEYWORDS: GI tract anastomosis, anastomotic leak, protective stoma, fibrin glue, perioperative nutrition, collagen matrix coated with the fibrinogen and thrombin

ANASTOMOTIC LEAK – RISK FACTORS

Intestinal anastomotic leak and the associated clinical problems is a complex and heterogeneous issue. Even defining a leak unambiguously is practically impossible – in one analysis regarding the attempts to define it, it was established that at least 56 definitions can be found in the literature, 13 of them referring to the upper gastrointestinal tract, 14 – biliary tree and pancreas, while 29 relating to the lower gastrointestinal tract [1]. Definitions are usually a compilation of certain anatomical and clinical features, considering diagnostic imaging results or metabolic consequences. It seems that one of the most accepted and relatively unequivocal definitions is the modified definition based on recommendations by the International Study Group of Rectal Cancer [2]. According to that definition, a leak is a defect of intestinal wall continuity at the level of an anastomosis that leads to the lumen communicating with surrounding space. Three degrees of leaks are distinguished: A – mainly radiological leak, clinical and biochemical symptoms are minimal, general condition does not necessitate intensive care; B – patients require intensive care but no need for laparotomy; C – the patient’s general state is very severe, and surgical intervention is required. From clinical perspective, B and C degrees are important.

In esophageal surgery, a leak is defined as ‘a transmural discontinuity within the line of surgical sutures, which leads to a clinically undesirable connection between lumens of the joined organs and surrounding anatomical or tissue space’. A leak can have a clinical character when the contents exit through a wound, drain, collect near the anastomosis or cause fever, lead to development or an abscess, phlegmon, sepsis, metabolic disorders and/or multiple organ dysfunction [1]. A leak that is confirmed by imaging studies but asymptomatic is referred to as a subclinical leak. In esophageal surgery, various classifications of leaks are used, distinguishing between subclinical and symptomatic according to Csendes (1990) and Deshmane (1994), radiological (minimal), symptomatic (moderate), severe with necrosis (Bardini, 1994), slight and considerable (Isozaki classification, 1994) and accidentally diagnosed, slight and considerable (Nambirjana scale, 1998) [13].

The prevalence of an intestinal anastomotic leak is remarkably varied and is between 1% up to even 50% depending on location, risk factors and diagnostic criteria [3,4,5,6,7,8,9]. It is an obvious fact that with such disparities regarding leak prevalence, risk factors are being searched for. Determination of such factors has a prognostic value (risk estimation of developing a leak), but also it allows to eliminate certain risk factors. Certainly, only some factors can be eliminated, in which case patient’s or physician’s actions may have a positive effect by reducing the leak rate. Identification of those factors is not easy. Examples of risk factors of an intestinal anastomotic leak are shown in Table 1.

It should be emphasized that, despite a large number of various studies (retrospective, prospective, reviews) indicating the role of many risk factors, it is extremely hard to find generally accepted risk factors considering their influence on an anastomotic leak. In large-scale metaanalyses on colorectal surgery, it was established that only 3 factors do have a unanimously confirmed role in development of an anastomotic leak, including ASA ≥3, prolonged surgery time over 180
From the risk factors mentioned above, smoking is a confirmed risk factor for both the upper [33] and lower [34] gastrointestinal tract. Recently, a greater role was attributed to the factors dependent on the medical team, where the role of the anaesthesiologist is highlighted in addition to the surgeon’s role. The perioperative course (body’s temperature, blood pressure, fluid balance) may determine, to a great extent, the risk of an intestinal anastomotic leak.

The search for an optimal model of factor analysis of anastomotic leak risk continues. It seems that searching for more complex interactions between risk factors and their full multivariate analysis is vital. For this purpose, a different kind of prognostic indices and risk calculators are being created. One of such tools is the PROCOLE index, which can be applied in colorectal surgery [36]. This index is based on a meta-analysis of previous research and includes the following: albumins level < 3.5; comorbidities (other severe and active systemic diseases, e.g. diseases of the kidneys, liver and peripheral vessels); preoperative leukocytosis; steroid therapy during surgery or immediately before it; lesion location/planned extent of resection; emergency indications; ASA 3 and more; estimated time of surgery; neoadjuvant therapy prior to surgery; diabetes; preoperative anaemia (Hgb < 11 ml/dl); chronic renal failure; male sex; cigarette smoking.

It seems that improving effectiveness of risk factor estimation for an anastomotic leak requires tools enabling:
- Prospective evaluation of treatment
- Mass (cohort) character of data collection
- Clear evaluation of selected risk factors
- Monitoring of treatment outcomes with particular emphasis on anastomosis leaks
- Fast and easy data entry by the physician
- Continuous analysis of the entered data

The authors of this article are currently developing an application, which is going to be a tool for estimation of leak risk (based on the analysis of the identified risk factors, mainly those included in the PROCOLE index), and at the same time they analyse risk factors and their influence on treatment (a mass prospective study). We hope that developing application with the working name “MedigenLeak” will become not only a useful research tool, but it will also support surgeons in perioperative decision making. Despite the fact that an anastomosis leak is often treated like a ‘quirk of fate’ or an independent complication, there are many real possibilities to significantly decrease the rate of this complication.

PREVENTION OF INTESTINAL ANASTOMOTIC LEAK – CURRENT METHODS

Potential methods of preventing intestinal anastomotic leaks include, to a great extent, quite obvious interventions, which may even seem trivial, however, keeping them in mind positively influences therapeutic outcomes.

Consider adding information regarding ERAS protocol

Currently in the literature, the importance of leak prevention and perioperative management according to the ERAS protocol (Enhanced Recovery After Surgery). Due to introduction of the ERAS rules, it was possible to achieve reduction in postoperative complication rate including smaller number of anastomotic leaks [37,38].

If only it is possible, especially when there is enough time between qualification and surgery, it is recommended to educate the patient making him aware that his actions may affect the overall outcomes. Certainly, in oncologic surgery, there is very little time between diagnosis/qualification and surgery, however, there are certain situations in oncologic surgery (e.g. preoperative radiochemotherapy of rectal cancer – 7-8 weeks, or esophageal cancer – 2 cycles of radiotherapy + a month of chemotherapy + 4-6 weeks of recovery after neoadjuvant treatment) or non-oncologic indications (i.e. restoring continuity of gastrointestinal tract after Hartmann’s operation), when waiting for surgery can allow for e.g. smoking cessation.

In addition to the listed actions, there are certain more ‘targeted’ interventions, which can strongly decrease the rate of anastomotic leak. Selected potential prophylactic methods are presented below.

- protective stoma

Formation of a protective (decompressing) stoma is a perfectly known strategy in colorectal surgery. For a long time, the topic was discussed regarding the influence of the protective stoma on healing of an anastomosis. It was a popular view that stoma formation allows to limit intensity of leak symptoms and decrease reoperation rate, while it does not directly influence leak rate. Nowadays, it is known that a stoma not only minimizes consequences of anastomotic dys-function, but also decreases the rate of anastomotic leaks [39]. Detailed discussion of indications for protective stoma formation and the recommended management are beyond the scope of this article, however, they constitute the basis for Polish consensus on protective stoma [40] and the monograph on stoma [41].

- proper nutrition

The influence of adequate nutrition on healing, including normal healing of intestinal anastomoses, is a well-known fact, which has been confirmed in multiple studies [42]. Preoperative albumin level is one of the most important factors affecting anastomotic leak development [43]. Proper nutritional preparation, which is an integral part of prevention of complications in gastrointestinal surgery [44], is also a very vast topic covered in many publications. One of the present-day recommendations is the Polish nutritional consensus in oncologic surgery, in which practical aspects of nutritional treatment is discussed in detail [45].

- surgical intervention

Obviously, introduction of certain surgical procedures can also be a factor decreasing the risk of an anastomotic leak. Examples include interventions used in esophageal surgery, such as delayed primary closure of a gastroesophageal or esophagoin-
There are also reports of a positive effect of cyanoacrylate and fibrin adhesives in preventing an anastomotic leak, in both experimental and clinical models [51]. In colorectal surgery, good results were observed applying cyanoacrylate adhesive to anastomoses with an increased risk of leakage [52]. Also, application of fibrin adhesive was an effective strategy in colorectal surgery, bariatric surgery or operations of the pancreas (although to a lesser degree) [53].

The results of studies regarding the efficacy of medical adhesives are equivocal, and in recent reviews, the ambiguity of the effectiveness and practical usefulness of medical adhesives has been emphasized; the positive effect can be attributed to strengthening the anastomosis rather than influencing healing [54], which has been confirmed by pathology studies of anastomoses in experimental models [54]. In the literature, there are reports of an increased risk of anastomotic stricture after application of acrylic adhesives, which can strongly influence therapeutic outcomes [55].

- rectal decompressing drainage in colorectal surgery

This strategy is associated with a decreased pressure in the alimentary tract. It results in lowered tissue tension and potentially, it facilitates healing [56]. However, data confirming the efficacy of this treatment are based on very little number of studies and there are still not enough data to recommend introduction of rec-
Fibrinogen is converted into fibrin monomers, application of collagen matrix covered with fibrinogen and thrombin [69], since the preliminary unpublished results are very promising. It seems that endoscopic vacuum therapy can be successfully used in prevention of upper gastrointestinal tract anastomotic leaks [68]. It seems that endoscopic vacuum therapy is used, which is particularly useful in esophageal and colorectal surgery. According to current beliefs, gastric tube is no longer justified as prophylaxis of an anastomotic leak [59]. Patients, who did not receive routine tube placement after an abdominal procedure, were characterized by faster return of peristalsis, lower rate of respiratory complications and a lower rate of the operated site infection (although the difference was not significant) [60]. No differences were found as to the anastomotic leak rate between patient with gastric tube and those without it [59,60].

- **gastric tube placement**

The foundation of this prophylactic method is similar to rectal decompressing drainage in colorectal surgery. The point is to mechanically decompress the alimentary tract, and placing the gastric tube is also associated with decompression of remaining gastric or intestinal content. According to current beliefs, gastric tube is no longer justified as prophylaxis of an anastomotic leak [59]. Patients, who did not receive routine tube placement after an abdominal procedure, were characterized by faster return of peristalsis, lower rate of respiratory complications and a lower rate of the operated site infection (although the difference was not significant) [60]. No differences were found as to the anastomotic leak rate between patient with gastric tube and those without it [59,60].

**Tab. II.** Selected patient- and surgeon-dependent risk factors of an anastomotic leak.

<table>
<thead>
<tr>
<th>Patient-dependent (patient-associated) risk factors</th>
<th>Disease-associated risk factors</th>
<th>Treatment-associated risk factors (usually referring to the surgeon)</th>
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<tbody>
<tr>
<td>age, sex, hemoglobin level, erythrocyte and leukocyte count; decreased albumin serum level, previous surgeries; prolongs steroid therapy, BMI &gt; 25; smoking; diabetes; quality of patient preparation (bowel cleansing); ASA &gt; 2; location of tumor (in the case of anterior lower resection of rectum), malnutrition, local inflammation or infection due to tumor/diverticular perforation; ileus below tumor level.</td>
<td>Neoplastic vs. non-neoplastic disease; inflammatory disease; vascular disease; advanced cancer (pTNM); previous oncologic treatment (chemotherapy and/or radiotherapy)</td>
<td>transfusion of &gt; 2 units of packed red blood cells; use of &gt; 2 staples; formation of anastomosis (type of anastomosis, type of sutures, number of layers); surgeon's experience (number of surgeries performed per year, years since specializing); mode of conduction (emergency); reference level of the hospital, peroperative nutrition, intraoperative hypotension, quality of joined intestines, lack of thorough hemostasis; no techniques to minimize leak risk (i.e. collagen matrix covered with fibrinogen and thrombin)</td>
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- **application of anastomotic ‘splint’ stents**

Stents are mostly used in gastrointestinal surgery for early treatment of a symptomatic anastomotic leak [61]. It is an effective strategy in both upper [61] and lower [62] gastrointestinal tract as well as biliary tree [63]. The results of the most recent studies seem to not only confirm a very positive effect of stent application on early treatment of gastrointestinal anastomotic leaks [64] and their role in endoscopic interventions [65], but also they indicate potential future methods of prophylaxis [66,67]. Currently, there are no recommendations regarding prophylactic use of stents to reduce intestinal anastomotic leak rate.

It is worth mentioning that as a more and more common alternative to stenting, the endoscopic vacuum therapy is used, which is particularly useful in esophageal and colorectal surgery. Endoscopic vacuum therapy in early interventions is characterized by greater efficacy with lower complication rate compared to stenting [68]. It seems that endoscopic vacuum therapy can be successfully used in prevention of upper gastrointestinal tract anastomotic leaks [69], since the preliminary unpublished results are very promising.

- **application of collagen matrix covered with fibrinogen and thrombin (TachoSil)**

This product utilizes natural hemostatic mechanisms. Fibrinogen and thrombin in the form of a dry layer on a collagen sponge (TachoSil) dissolve when contacted by body fluids and penetrate the surface of the wound. Next, a reaction between fibrinogen and thrombin takes place, which initiates the last phase of physiological coagulation. Fibrinogen is converted into fibrin monomers, which polymerize spontaneously forming a clot. The clot adheres strictly to the wound surface and causes the collagen sponge to adhere. It leads to a strong hemostatic and tightening effect. For this reason, the matrix can be used to seal an intestinal anastomosis. In the next stage, fibrin, which is bound by the endogenic factor XII, forms a strong, mechanically stable net. Due to robustness and strong adhesion, this structure supports and seals the anastomosis. Sealing properties of TachoSil have been confirmed in clinical studies [70,71] in thoracic surgery, where it is used to decrease the postoperative risk of air leakage, as well as neurosurgery, where TachoSil has been shown to be effective in preventing cerebrospinal fluid leakage [72].

The efficacy of TachoSil in gastrointestinal surgery has been well-documented in animal models, for both the lower [73,74] and upper [75] gastrointestinal tract. Of upmost importance is leak prevention in the case of anastomoses at risk of abnormal healing, e.g. with concurrent chemotherapy [76], narrow lumen [77] or even in perforation treatment [78]. The authors of those studies emphasize the safety of collagen sponges covered with fibrinogen and thrombin [79] and their simple use [80].

Such promising results have urged many surgeons to use this product in their clinical practice. Its efficacy has been confirmed for both lower [81] and upper [82] gastrointestinal tract, as well as in emergency cases and high risk of leak [82]. Also, in clinical practice, the application of the sponge is simple and safe [84].

In liver surgery, despite its confirmed hemostatic role, TachoSil diminished bile leakage as well [85]. TachoSil can be particularly useful in extended liver resection [86], decreasing bile leakage after surgery [87,88]. In pancreatic surgery, TachoSil can be safely applied to the remaining pancreas after its peripheral resection as a safe intervention, however, there are no data confirming that its use decreases the rate of postoperative pancreatic fistula, mortality, reoperation rate, blood loss and hospital stay [89]. It seems that collagen matrix covered with fibrinogen and thrombin can play a significant role in prevention of intestinal anastomotic leaks, especially in patients with multiple risk factors.

In addition to methods mentioned above, there are many single reports about usage of different techniques or concepts of ‘hardening’ the anastomosis, which can play a role in decreasing the risk of an anastomotic leak, for example application of fetal membranes to cover an anastomosis with patients at high risk of a leak [90]. Esophageal surgery shows tissue engineering with esophageal replacement by cellular and non-cellular transplants (patch / esophageal tube), with a matrix made of epithelial and smooth muscle cells, as well as functional endothelial and Cajal cells, which are nowadays, however, a distant vision.
It seems, that search for effective prophylactic methods in gastrointestinal surgery has just started, although it should be emphasized that in the case of colorectal surgery, formation of a protective stoma is the most common and widely accepted procedure. Potentially effective preventive measures may be general (perioperative nutrition, smoking cessation) as well as local (tissue adhesives, collagen matrix covered with fibrinogen and thrombin). Considering validity and legality of additional (preventive) interventions during anastomosis formation, it should be mentioned that currently there are no precisely defined standard for ending a gastrointestinal operation. The previously mentioned procedures can end with an intestinal anastomosis, stoma formation with no anastomosis, an anastomosis with proximal decompressing stoma. The physician, who makes the decision for an additional intervention (e.g. to use TachoSil or tissue adhesive) due to the suspicion of a possible anastomotic leak is not responsible for ‘malpractice’. Preventive use of TachoSil in order to assure the optimal effect (obtaining the maximum anastomotic seal in an individual case) provides due diligence, which is a result of using the optimal techniques available.

In the near future, a high interest in the subject of anastomoses following intestinal resection is to be expected. On the one hand, an anastomotic leak is the most serious complication of a surgery, which is still associated with a high mortality rate. On the other hand, we now better understand the role of determination of risk factors. It results in e.g. developing the above-mentioned PROCOLE index, expert teams, including for instance the team of the authors of this article or the International Multispecialty Anastomotic Leak Global Improvement Exchange group formed in 2016 and led by SD Wexner [91]. The next important aspect is the rising number of possible methods or drugs improving anastomotic sealing, resulting not only in an increased comfort of the surgeon, but mainly in lower complication rate and better quality of life of patients.

REFERENCES


