Clinical Science

Mediastinal microdialysis in the diagnosis of early anastomotic leakage after resection for cancer of the esophagus and gastroesophageal junction

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KEYWORDS:
Mediastinal microdialysis; Anastomotic leakage; Esophageal cancer; Lactate/glucose ratio; Lactate/pyruvate ratio

Abstract

BACKGROUND: Anastomotic leakage (AL) after gastroesophageal resection for cancer is a serious complication. The aim was to evaluate mediastinal microdialysis in the detection of AL before clinical symptoms.

METHODS: Sixty patients were included. Samples were collected every 4 hours in the 1st 8 postoperative days and analyzed for several metabolites.

RESULTS: Forty-four patients had an uncomplicated postoperative recovery, 7 developed anastomotic-related complications, and 5 developed major nonanastomotic-related complications. Six patients were excluded (early catheter malfunction and reoperation). Logistic regression model on several metabolites demonstrated a 100% sensitivity, specificity, and positive and negative predictive values regarding the diagnosis of anastomotic complications within postoperative day 7. However, as independent markers, none of the measured metabolites were able to predict AL.

CONCLUSION: The diagnosis of anastomotic-related complications before clinical symptoms seemed possible by mediastinal microdialysis, but the diagnosis should be based on an interpretation of several metabolic events.

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Anastomotic leakage (AL) after gastroesophageal (GE) resection for cancer is a serious and challenging complication with a high morbidity and mortality. The incidence of AL is reported to be between 4% and 9%, and is responsible for up to 35% of postoperative deaths.1–6 AL may be divided into 2 categories according to the time from surgery to occurrence of the leakage: early between postoperative day 1 and 7 and late after the 7th postoperative day. Diagnosis and treatment of the AL will often depend on this categorization, but early diagnosis and intervention are critical in all cases to improve outcome.7 Nonoperative strategies including covered stents, gastric tubes, additional chest tubes, broad-spectrum antibiotics, and oral decontamination have a high success rate in the early phase of an AL. Thus, early detection remains the most important factor for a successful result irrespective of the overall treatment strategy.

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The diagnosis of AL is primarily based on clinical symptoms and elevated inflammatory parameters in blood samples. However, the diagnostic specificity and accuracy are low with a significant delay. More invasive procedures like endoscopy and fluoroscopy have a higher specificity and accuracy, but are not an option for continuous postoperative surveillance, and may not confirm the AL until mediastinal contamination has become a threat to the patient. Many factors may predispose to AL, but ischemia in the anastomotic area is believed to be one of the most important factors.

Microdialysis is a semi-invasive method that may monitor local metabolism and thereby indirectly monitor ischemia of the gastrointestinal tract following surgery. The microdialysis technique allows continuous monitoring of the concentration of molecules of interest in the mediastinum and subcutis by introducing a catheter with a tubular semipermeable dialysis membrane. The catheter is perfused with a Ringer’s solution, which equilibrates over the membrane with the molecules in the surrounding fluid. In animal studies and in a few human studies, intraperitoneal microdialysis has been able to detect AL before the development of significant clinical symptoms, and the lactate/pyruvate ratio (L/P ratio) is the parameter, which has demonstrated the highest sensitivity so far. To our knowledge, no studies have been performed using this technique in primary GE anastomosis after resection for cancer, except in our preliminary trial. However, a study on free jejunal flap for esophageal reconstruction in high-located cancers has demonstrated promising results.

Our hypothesis is that mediastinal microdialysis (MM) is able to detect AL before the development of significant clinical symptoms or rising inflammatory parameters in peripheral blood.

The aim of this study is as follows:

1. To evaluate the safety and results of mediastinal and subcutaneous microdialysis in patients undergoing GE resection for cancer
2. To study the potential differences of the microdialysis results in uncomplicated and complicated cases
3. To evaluate if early AL would provide significant changes in the microdialysis results before clinical symptoms, and to determine potential cutoff values

**Patients and Methods**

Sixty nonconsecutive patients who had surgery for cancer of the lower part of the esophagus or the GE junction were included in this prospective study. All patients were operated at our department in the period from June 2006 to April 2010. The operation was a 3-step procedure, including laparoscopy and laparoscopic ultrasound to evaluate stage and resectability before laparotomy and right-sided thoracotomy (Ivor–Lewis resection). One patient had a colonic interposition, while the rest of the patients had a standard gastric pull-up procedure. All patients received a chest tube (CH 18) placed close to the anastomosis. The chest tube as well as a gastric tube were kept in place until the day after the standard water-soluble contrast examination of the anastomosis, which was performed on the 7th postoperative day. The tubes were left in place in cases with confirmed or suspected AL.

**Mediastinal and subcutaneous microdialysis**

A 310-mm long microdialysis catheter (CMA 61, M Dialysis, Sweden) was placed in the right pleural cavity through a separate percutaneous puncture. The catheter was fixed to the pleura with a 4-0 absorbable suture near the anastomosis to ensure its position. A 54-mm long subcutaneous microdialysis catheter (CMA 60, M Dialysis, Sweden) was placed in the pectoral region and served as a reference. Both catheters consisted of a 1-mm thin double-lumen plastic tube with a 30-mm semipermeable tubular membrane at the distal end. The membrane has a cutoff at 20,000 D. Fluid (Perfusion fluid T1, M Dialysis, Sweden) was infused through each catheter via a portable mini pump (CMA 106, M Dialysis, Sweden) with a flow rate of .3 μL/hour. Samples were collected every 4 hours for a maximum of 8 consecutive days after surgery and stored at −20°C. The catheter may malfunction in the early phase because of protein deposits on the membrane, and the function of the catheter is not guaranteed by the company beyond 5 days.

If an early leak could not be detected within the 1st 4 postoperative days, we would find the method unsuitable for clinical use. Therefore, only data from the 1st 4 postoperative days were used in the calculations for early leakage. Samples were analyzed within 5 days for the concentration of lactate, pyruvate, glucose, and glycerol (ISCUS Microdialysis Analyser, M Dialysis, Sweden). The L/P and L/G (lactate/glucose) ratios were calculated.

All patients were closely monitored regarding any clinical symptom or alterations in blood samples indicating complications. Blood samples were not routinely performed on a daily basis. If AL was suspected, a computed tomography (CT) scan with oral contrast was performed followed by endoscopy. Each patient was assigned to one of the 3 different complications categories: uncomplicated (or with minor complications only) complications, major complications not related to the anastomosis, and complications related to AL. The anastomotic-related complications group was divided into early AL defined as before the 8th postoperative day and late AL defined as occurring after the 7th postoperative day.

Complications related to the microdialysis procedure were registered separately. The identification and treatment of the ALs followed the department’s standard procedures.

The local Ethics Committee approved the study and all patients gave informed consent before inclusion.

**Statistical analysis**

The overall analysis of data was based on repeated measurements of the 4 parameters in the microdialysis fluid.
Table 1  Demographics, tumor characteristics, and surgical outcome in a total of 54 patients undergoing resection (no significant differences between the 2 groups)

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
<th>No complications and nonanastomotic-related complications (n\textsubscript{patients} = 47)</th>
<th>Anastomotic-related complications (n\textsubscript{patients} = 7)</th>
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</thead>
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<tr>
<td>Demographic data</td>
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<td>60 (45–80)</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>Men</td>
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<tr>
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<td>Former smoker</td>
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<td>3</td>
<td>2</td>
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<td></td>
<td>No</td>
<td>44</td>
<td>5</td>
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<tr>
<td></td>
<td>Preoperative BMI (mean and range)</td>
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<td>8</td>
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<tr>
<td></td>
<td>II</td>
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<td>5</td>
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<tr>
<td></td>
<td>III</td>
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<tr>
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<td>Distance from the row of teeth in cm,† mean (range)</td>
<td>35 (24–43)</td>
<td>37 (37–44)</td>
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<td></td>
<td>Preoperative chemotherapy</td>
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<tr>
<td></td>
<td>Yes</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Surgical data</td>
<td>Mean length of surgical procedure in min</td>
<td>354 (260–478)</td>
<td>365 (270–465)</td>
</tr>
<tr>
<td></td>
<td>Mean intraoperative bleeding in mL</td>
<td>1,052 (170–3,600)</td>
<td>930 (260–2,600)</td>
</tr>
</tbody>
</table>

\( \chi \) = Maximal recommended limits (units per week) for males is 21 and 14 for females (Danish Health Authorities).

ASA = American Society of Anesthesiologists score; BMI = body mass index.

*Data missing in 5 patients.

†Data missing in 1 patient.

Data missing in 2 patients.
Data obtained during the 1st 4 postoperative days were used when considering early anastomotic-related complications, whereas the analysis of all anastomotic-related complications used all available measurements.

**Descriptive analysis**

Descriptive and curve trends analysis were made for the curves of each patient and parameter.

**Area under the curve**

Area under the curve (AUC) and Wilcoxon signed-rank test were used to test for difference in the microdialysis results between the groups with and without anastomotic complications.

**Descriptive models, logistic regression models, and receiver operating characteristic (ROC) curves**

Since the measured values for each parameter fluctuate across the observation period, the maximum and minimum values for each parameter were used as well. Thus, these values were included in the models based on the theoretical background of microdialysis (eg, both the low and high values of glucose may reflect changes in the metabolism) and based on the experience from other studies.

Different descriptive models were established using aggregates of measurements, and logistic regression models were then made to evaluate the different measurements. Based on the logistic regression models, ROC curves were used to define the optimal cutoff point to get a high specificity and sensitivity. The predictive values of the different aggregates and logistic models were then tested.

In the clinical setting analysis of the full range of data is not a feasible approach. Instead, the data should be evaluated after each measurement to detect anastomotic complication as early as possible, and this aspect was given consideration in the design of the models. Likewise, the time of the 1st positive test using the best model was evaluated and compared with the time of clinical detection of an anastomotic complication.

**Categorical data**

Categorical variables were compared with Fisher’s exact test. \( p < .05 \) were considered statistically significant. Statistical calculations were performed using the Stata version 11 (StataCorp LP, College Station, TX).

**Results**

Of the 60 patients who were included, 6 patients were excluded immediately after surgery: 5 patients due to catheter malfunction and 1 patient due to early reoperation because of an intercostal artery lesion following catheter insertion. The remaining 54 patients consisted of 48 men and 6 women with a median age of 60 years (range 40 to 80) and 66 years (60 to 75), respectively. Seven patients (11.7%) had an AL-related complication: 3 patients with early leakage, 3 with a late leakage, and 1 patient with a late esophagobronchial fistula (diagnosed and treated on the 9th day).
Reoperation was necessary in 2 cases, while the remaining patients were treated either conservatively or with self-expandable metallic stent. Five patients had serious nonanastomotic-related complications, which in 2 cases required intensive care and in 1 case the complication was fatal because of acute respiratory distress syndrome and multiple embolism. Forty-four patients had an uneventful postoperative recovery with only minor complications. Patients with and without anastomotic-related complications were comparable regarding demographic data and tumor characteristics (Table 1). All minor and major postoperative complications and their treatment are listed in Table 2.

Complications to the microdialysis

One serious adverse event was observed. An intercostal artery was hit during placement of a MM catheter and the patient was reoperated because of bleeding. Otherwise no catheter-related complications were observed.

Microdialysis time and missing values

The median number of days with a functional microdialysis catheter was 7.2, and 90% had a catheter for 4.8 days. Eleven patients (20%) had no missing values, but on average patients had 10% missing values. Time and cause of drop out are shown in Fig. 1.

Subcutaneous microdialysis and uncomplicated courses

The values from mediastinal and subcutaneous microdialysis for the 1st 4 postoperative days showed a significant difference in all parameters. No significant differences in the subcutaneous parameters were observed between the group of patients with an uncomplicated course compared to the patients with anastomotic-related complications or other major complications (Table 3).

Detection of anastomotic leakage

The AUC for the mediastinal lactate measurements was significantly higher for the patients with complications than for the patients without complications ($P = .04$). There was no significant difference in AUC between the 2 groups for any other parameter measured in the mediastinum or subcutis. For the detection of an anastomotic complication only mediastinal data were used since there were no significant differences between the subcutaneous measurements in the different clinical situations. The sensitivity and specificity for L/P and L/G ratios in the subgroup of early anastomotic complications and in all cases of anastomotic complications are demonstrated in Figs. 2, 3 and Table 4. These ratios proved to be the best 2 single parameters to detect early leakage. The correlating diagnostic test showed a positive predictive value (PPV) and negative predictive value (NPV) for the L/G ratio of 43% and 100%, and for L/P ratio of 50% and 100%, respectively (Table 4). Regarding all anastomotic complications, the PPV and NPV for the L/P ratio and L/G ratio were 29%, 93%, 57%, and 94%, respectively (Table 4).

A logistic regression model based on maximum L/G and L/P ratios and the minimum and maximum measured values of lactate, pyruvate, and glucose were established. Glycerol improved the model for all anastomotic complications and was included in the calculation. However, it did

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**Table 3** Values of mediastinal and subcutaneous microdialysis in the group without complications and the group with anastomotic-related complications

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No complications and nonanastomotic-related complications ($n_{\text{patients}} = 47$)</th>
<th>Anastomotic-related complications ($n_{\text{patients}} = 7$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n_{\text{samples}} = 1,710$ mean (SD)</td>
<td>$n_{\text{samples}} = 253$ mean (SD)</td>
</tr>
<tr>
<td>Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L/P ratio</td>
<td>25.5 (21.0)</td>
<td>61.5 (120.9)</td>
</tr>
<tr>
<td>L/G ratio</td>
<td>1.01 (3.01)</td>
<td>33.3 (27.7)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>6.5 (2.5)</td>
<td>5.4 (2.5)</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.9 (2.5)</td>
<td>5.8 (4.5)</td>
</tr>
<tr>
<td>Pyruvate (mmol/L)</td>
<td>162 (58)</td>
<td>156 (65)</td>
</tr>
<tr>
<td>Glycerol (μmol/L)</td>
<td>54 (51)</td>
<td>45 (45)</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L/P ratio</td>
<td>13.3 (5.5)</td>
<td>13.1 (5.2)</td>
</tr>
<tr>
<td>L/G ratio</td>
<td>.27 (.20)</td>
<td>.31 (.18)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>7.4 (2.0)</td>
<td>6.4 (1.7)</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.9 (1.0)</td>
<td>1.9 (1.3)</td>
</tr>
<tr>
<td>Pyruvate (mmol/L)</td>
<td>143 (57)</td>
<td>149 (52)</td>
</tr>
<tr>
<td>Glycerol (μmol/L)</td>
<td>253.4 (107.7)</td>
<td>307 (173)</td>
</tr>
</tbody>
</table>

$L/G = \text{lactate/glucose}; L/P = \text{lactate/pyruvate}; \text{SD} = \text{standard deviation.}$
not alter the model for the early anastomotic complications and was therefore omitted. Using the predicted probability from the model, ROC curves were made and the sensitivity and specificity were found to be 100% in the early anastomotic complications group and 86% and 96% in the group of all anastomotic complications, respectively (Fig. 3A,B). The PPV and NPV were 100% in the case of early anastomotic complications, and 75% and 98% in the case of all anastomotic complications (Table 4). Table 5 shows the day of the positive tests based on the logistic regression model for all anastomotic complications compared to the day of the clinical detection. Six out of the 7 anastomotic-related complications had a positive test. In most cases, the test was positive up to several days before the leakage was clinically recognized, and this was often within the first few days of the monitoring period. Two patients had a positive test at day 5 and 6: Atrial fibrillation was observed in one of the cases, but none of them had anastomotic-related or other major complications. If the same evaluation was performed on maximum L/G or L/P ratios only, a positive test would have been missed in 3 cases with anastomotic-related complications.

**Comments**

AL after GE resection for cancer is a serious complication with a high morbidity and mortality rate. Early diagnosis and control of the septic focus may reduce the severity of the mediastinitis and thereby improve prognosis, but the insidious presentation of AL with nonspecific symptoms similar to other postoperative complications makes the diagnosis difficult. As for the diagnosis of an AL, there are several methods including radiological examination, oral administration of methylene blue, and endoscopic examination. But these procedures may only be performed when the clinical condition indicates an AL, at which point the patient is already contaminated.

To our knowledge, it has not previously been attempted to establish a local biochemical monitoring method to diagnose preclinical, intrathoracic AL, except by Sorensen et al and in our preliminary study. Tang et al demonstrated that placing a drainage tube adjacent to the esophageal anastomosis at the time of surgery was a good method to diagnose and treat leakage. However, this method recognized only manifest leaks, while MM may
have the potential of diagnosing preclinical AL because of
continued local monitoring of the environment near the
anastomosis.

Complications to the microdialysis

Despite one serious complication (bleeding from a
lacerated intercostal artery), we consider mediastinal and
subcutaneous microdialysis to be safe methods.

Microdialysis time and missing values

One of the problems with the method was a fairly high
amount of missing values. This was explained by catheter
malfunction, catheter removed by accident, missing sam-
ples over short periods, or lack of change of the collecting
vials by the nursing staff. Whether these missing values
may have impaired the method is uncertain.

Our results indicate that MM for 4 to 5 days, only, would
provide the necessary results regarding the diagnosis of
anastomotic-related complications – and especially the
ey early ones. This was also consistent with the authorized
maximal durability of 5 days of the catheter.

Subcutaneous microdialysis and uncomplicated
courses

Subcutaneous microdialysis had no value as a reference
or diagnostic catheter since all parameters were stable and
within the same reference frame in both uncomplicated and
complicated cases. The same observation has been made in
patients operated for rectal cancer. The uncomplicated
courses had the same values and range over time as demon-
strated in intraperitoneal microdialysis.

Chylothorax and subclinical leakage with a
negative test

The patient with chylothorax in the group of
nonanastomotic-related complications had a high mean
glycerol level (95.3 µg/L) in the MM catheter compared
to both uncomplicated and complicated cases. This obser-
vation correlated to the expected increased lipid concen-
tration because of the contents of the chylos.

In 1 patient, MM indicated severe inflammation or
ischemia, but there were no clinical signs of AL. Overall
mean L/P ratio, lactate, and glucose was 118.3, 9.26, and
2.5 mmol/L, respectively, but the logistic regression model
was negative.

Two weeks after discharge an endoscopic examination
because of dysphagia demonstrated inflammation in the
anastomotic area, but there was no sign of AL. It may be
speculated that these biochemical changes were preceded
by a minor postoperative leak or ischemic episode.

Detection of anastomotic leakage

Using a logistic regression model in an optimal
biochemical setting, we found a 100% sensitivity, speci-
cificity, PPV, and NPV regarding the diagnosis of anasto-
matic complications within the 8th postoperative day. Using
the model on all anastomotic-related complications
provided a PPV of 75% and a NPV of 98% (Table 4). A pos-
itive test was demonstrated in 6 out of the 7 anastomotic-
related complications, and only 2 false-positive tests
were observed (Table 5). If maximum values of L/P or
L/G ratios were used alone, only 4 anastomotic-related
complications had a positive test, and 12 patients had a
false-positive test (data not shown). However, the L/G
and L/P ratios proved to be the best single parameter as
opposed to the other parameters (glucose, lactate, glycerol,
and pyruvate) which had no diagnostic value.

No positive test was seen in the group of 5 patients, who
developed serious nonanastomotic-related postoperative
complications (Table 2). This suggests that MM is a local
monitoring method and even severe complications with
ystemic influence will not influence this monitoring. In
this context, we believe that the consideration about the
location and fixation of the catheter in close proximity to
the anastomosis was ideal and fulfilled the purpose of local

Figure 3  ROC curves for logistic regression model separated
into all anastomotic complications (A) and anastomotic complica-
tions within 7 days (B).
monitoring. The location of the catheter was not routinely controlled, but this could have been done by a thoracic CT scan since the CMA 61 catheter contains a radiopaque marker at the tip.

The selected cutoff values were chosen with the purpose of making the false-positive group as small as possible (Table 4). A positive test in a clinical setup would have consequences like endoscopy procedures, CT scans, or reoperation which all may carry a potential risk.

The pathophysiological mechanism in AL after esophageal resection is not fully understood, but local ischemia seems to play a major role because of the insufficient blood supply of the conduit. Whether a local inflammation may cause perforation of the anastomosis as seen after rectum resection is unknown. In the presence of oxygen, glucose turns into pyruvate through oxidation with the production of energy in the form of ATP, and in the absence of oxygen, energy is produced by the reduction of pyruvate to lactate. Thus, ischemia will result in an increase in the L/P ratio, L/G ratio, lactate, and a decrease in glucose and pyruvate. Theoretically, the glycerol concentration could rise or fall. Apoptosis caused by ischemia will release glycerol from the cell membrane and the concentration would rise. Glycerol could also decrease in an ischemic condition caused by the stress hormone norepinephrine’s effect on the lipid metabolism.19,23 Whether this same pattern is seen in the inflammatory process is still unknown. In peritoneal microdialysis, it has been demonstrated that there is a significant lower glycerol concentration in patients with postoperative complications.23 From our regression model, the theoretical pattern related to the ischemic processes is almost fulfilled, and the few exceptions may coincide with – or even be a part of – the underlying inflammatory processes. The results suggest that the detection of anastomotic-related complications with microdialysis should be a confluence of metabolic events since no single parameter has enough diagnostic strength. The results also demonstrated that MM has no value in detecting nonanastomotic-related complications. Major issues that need to be addressed in future trials include testing of the established cutoff points in a larger closely monitored prospective AL study, the potential impact of continuous bedside MM as well as MM cost-benefit analyses. Perhaps the actual strength of MM lies in the ability to increase our knowledge regarding the local environment (eg, concentrations of antibiotics) rather than the preclinical detection of AL.

Limitations of the study

The regression analysis has limitations because it would require a mathematical model in everyday clinical practice. However, larger studies may establish more simple models and thus make the interpretation of data easier.

The statistical power, especially regarding the early AL, was limited because of the low number of cases.

<table>
<thead>
<tr>
<th>Table 5 Detection of all anastomotic complications using logistic regression model and compared with the day of the clinical detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case no.</td>
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χ = nonanastomotic complication or other major complications was observed.
Costs of the microdialysis

After having invested in a bedside analysis machine and the microdialysis pumps, the cost for 7 days of microdialysis in 1 patient with 1 catheter (6 samples a day) was 673.82 US dollars. Although it remains to be evaluated if early detection of AL by MM would provide a better outcome for the patient, we believe that this cost is low compared to the potential costs related to the treatment of complicated AL.

Conclusions

Results from this study showed that MM is a promising method to detect early AL before the development of significant clinical symptoms. The perspective will be early (nonsurgical) intervention with the potential to avoid severe morbidity and even mortalities from AL. Larger prospective studies with bedside analysis are necessary to establish sensitivity, specificity, PPV, and NPV at defined cutoff values as well as the potential clinical value of early intervention.

References