Outcome and treatment of acute diverticulitis
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Complicated diverticulitis in post-transplant patients, a systematic review.

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ABSTRACT

Background
Immunosuppression could increase the complication rate in patients with acute diverticulitis. This would justify a low threshold for elective sigmoid resection in these patients after an episode of diverticulitis. Well-documented groups of immunocompromised patients are transplant patients, in which many prospective studies have been conducted.

Objectives
The aim of this systematic review is to assess the incidence of complicated diverticulitis in post-transplant patients.

Data source
We searched MEDLINE, EMBASE, CINAHL and Cochrane databases for papers published between January 1966 and January 2014.

Study selection and intervention
Publications dealing with post-transplant patients and left-sided diverticulitis were eligible for inclusion. The following exclusion criteria were used for study selection: abstracts, case-series and non-English articles.

Main outcome measures
Primary outcome measure was the incidence of complicated diverticulitis. Secondary outcome was the incidence of acute diverticulitis and the proportion of complicated diverticulitis. Pooling of data was only performed when more than five reported on the outcome of interest with comparable cohorts.
RESULTS

Seventeen articles met the inclusion criteria. Nine renal transplant cohorts, four mixed lung-heart-heartlung transplant cohorts, two heart transplant cohorts, and two lung cohorts. A total of 11,966 post-transplant patients were included in the present review. Overall incidence of complicated diverticulitis in all transplantation studies ranged from 0.1 to 3.5%. Ten studies provided proportion of complicated diverticulitis. Pooled incidence of acute diverticulitis in these studies was 1.7% (95% CI: 1.0 to 2.7%). Pooled proportion of complicated diverticulitis among patients with acute diverticulitis was 40.1% (95% CI: 32.2 to 49.7%). All studies were of moderate quality using the MINORS scoring scale.

Conclusion

The incidence of complicated diverticulitis is about one in hundred transplant patients. If a transplant patient develops an episode of acute diverticulitis, a high proportion of patients has a complicated disease course.

Background

The incidence of acute diverticulitis is increasing in Western populations (1, 2). Most patients have an uncomplicated disease course (3). Perforated diverticulitis is uncommon, however, if perforation occurs, it is associated with high mortality rates (4, 5). Different studies have tried to identify patients at risk of developing perforations: older patients (4), patients with multiple co-morbidities (4, 5), patients on non-steroidal anti-inflammatory drugs (4, 6), and immunocompromised patients (7).

Different guidelines and reviews advise that immunocompromised patients should be offered an elective sigmoid resection after their first episode of acute diverticulitis (8, 9, 10). This advice is mostly based on uncontrolled cohort studies (7) and in a recent study this advice was disputed (11). Elective sigmoid resection for diverticular disease is not without risks. It can reach a mortality rate of 1.9% with a major morbidity rate of 25% (12).

Immunocompromised patients are patients such as transplant recipients, patients with diseases affecting the immune system and/or chronic use of drugs as corticosteroids. It is difficult to compare these patient groups, which has however frequently been done by various investigators (7, 13). Diseases affecting the immune system such as HIV/AIDS, haematological malignancies or genetic disorders occur mostly in relatively young patients (<40 years) or are rare. (14) The use of steroids is difficult to monitor and non-compliance is high (15). A more reliable group of immunocompromised patients to
study diverticulitis are transplant recipients. This is generally a well documented, com-
pliant group of patients with regular follow up. The number of post-transplant patients
and their survival is rising (16).

The aim of present review was to evaluate whether the incidence of complicated acute
diverticulitis is increased in transplant recipients, being a more or less homogenous
group of immunocompromised patients, compared to the general population.

METHODS

Literature search
Two authors (JO and CU) independently performed a literature search to identify studies
investigating diverticulitis in patients who have undergone organ transplantation. We
searched MEDLINE databases for papers published between January 1966 and Janu-
ary 2014, using the following keywords: ("Diverticulitis"(Mesh) AND ("Transplantation"
(Mesh)). Free text words were also used instead of Mesh terms to avoid missing recent
articles that had not yet been given a Mesh label. EMBASE database was searched
with the following terms: diverticulitis and transplantation. CINAHL database was
also checked for relevant studies with the following keywords: ("Diverticulitis" AND
"Transplantation"). The Cochrane database of Systematic Reviews was searched with the
following words: Diverticular disease.

The search was not restricted to any language, but in the systematic review, only stud-
ies published in English were taken into account.

Validity assessment
After identifying relevant titles, all abstracts were read and eligible articles were retrieved.
A manual cross-reference search of the references of relevant articles was performed to
identify other studies not found in the search. Only studies published in English were in-
cluded. No unpublished data were included. A full search strategy is available at request.
Two authors independently assessed the methodological quality of the articles using
the checklist of the Cochrane collaboration and MINORS quality score, with a global
ideal score of 16 for non-comparative studies and 24 for comparative studies (21).

Definition
Acute diverticulitis is complicated diverticular disease with clinical symptoms and
evidence of inflammation, confirmed by imaging. Complicated diverticulitis consists of
perforation, fistulae, abscess formation and stenosis. A patient was considered “post-
transplanted" if the patient had received a solid organ transplant (liver, lung, heart, kidney, and pancreas).

**Inclusion and exclusion criteria**

*Types of studies*
Articles were eligible for inclusion if the following criteria were met: publications dealing with post-transplant patients, left-sided diverticulitis, articles in English, human studies and available full text. The following exclusion criteria were used for study selection: case-series and abstracts.

*Types of participants*
Post-transplant patients with (complicated) diverticulitis were included.

*Types of outcome measures*
Primary outcome measure was the incidence of complicated diverticulitis. Secondary outcome was the incidence of acute diverticulitis and the proportion of complicated diverticulitis.

**Data analysis**
MetaAnalysist software version 3.1 was used for the meta-analysis. To provide a reliable outcome, and to gain sufficient homogeneity of the pooled data only six or more studies comparable were used for pooled analyses. For the primary outcome therefore only renal transplant studies were used. For the secondary outcome to gain sufficient studies we pooled all the studies that described proportion of complicated diverticulitis. Rates were pooled using a random-effects model. We determined the presence of heterogeneity between the studies by using a forest plot and by performing a \( \chi^2 \) ("chi-squared") heterogeneity test and the I\(^2\)–index was calculated.

**RESULTS**

*Description of studies*
The flowchart for the systematic review is shown in Figure 1. A total of 228 publications were initially identified in the literature search, from which 35 articles were retrieved for more detailed information. Electronic links to related articles and references of selected articles were hand searched as well. References were snowballed. A hand search of relevant journals and conference proceedings was not performed. Duplicate publications and papers that reported on (parts of) the same study population were excluded from
Chapter 4

After reading the 35 retrieved articles and the application of our inclusion criteria, we found 17 relevant articles. There was complete agreement among the authors as to the inclusion of these studies.

Included studies
The 17 included studies described a total of 11,966 post-transplant patients. Overall incidence of acute diverticulitis ranged from 0.4% to 6.2%. For complicated diverticulitis an incidence ranging from 0.1% to 3.5% was found within the total group of post-transplantation patients. The results are summarized in Table 1. All studies were of moderate quality using the MINORS scoring scale. (Table 2)
## Table 1. Included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Type of transplantation</th>
<th>Immunosuppressive therapy</th>
<th>Acute diverticulitis</th>
<th>Complicated diverticulitis</th>
<th>Mortality¹</th>
<th>MINORS^</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Paul et al, 2009</td>
<td>208</td>
<td>N/A</td>
<td>LTx, HTLx</td>
<td>(ATG+MP+C) or (T+A/MMF)</td>
<td>3 (1.4%)</td>
<td>1 (0.5%)</td>
<td>1 (100%)</td>
<td>9</td>
</tr>
<tr>
<td>2. Coccolini et al, 2009</td>
<td>1651</td>
<td>N/A</td>
<td>RTx</td>
<td>S</td>
<td>N/A</td>
<td>14 (0.8%)</td>
<td>N/A</td>
<td>8</td>
</tr>
<tr>
<td>3. Goldberg et al, 2006</td>
<td>1012</td>
<td>52.6 (20-71)</td>
<td>HTx, LTx, HTLx</td>
<td>(P+C) / or (T/A/ MMF/R)</td>
<td>14 (1.4%)</td>
<td>3 (0.3%)</td>
<td>N/A</td>
<td>10</td>
</tr>
<tr>
<td>4. DallaValle et al, 2005</td>
<td>875</td>
<td>49.5*</td>
<td>RTx</td>
<td>Tripledrug therapy</td>
<td>N/A</td>
<td>8 (0.9%)</td>
<td>1 (12.5%)</td>
<td>10</td>
</tr>
<tr>
<td>5. Qasabian et al, 2004</td>
<td>953</td>
<td>48.5 (11-65)*</td>
<td>HTx, LTx, HTLx</td>
<td>P and/or A and/ or C</td>
<td>N/A</td>
<td>9 (0.9%)</td>
<td>1 (12.5%)</td>
<td>10</td>
</tr>
<tr>
<td>6. Hoekstra et al, 2001</td>
<td>125</td>
<td>43 (9-64) #</td>
<td>LTx</td>
<td>P+A+C (after induction)</td>
<td>N/A</td>
<td>5 (4%)</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>7. Khan et al, 2001</td>
<td>268</td>
<td>49.8 (9) *</td>
<td>HTx, LTx</td>
<td>ATG+P+A+C</td>
<td>2 (0.7%)</td>
<td>2 (0.7%)</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>8. Maurer et al, 2000</td>
<td>210</td>
<td>44 (2-64) *</td>
<td>LTx</td>
<td>P+A+C</td>
<td>3 (1.4%)</td>
<td>6 (2.9%)</td>
<td>N/A</td>
<td>9</td>
</tr>
<tr>
<td>9. Mueller et al, 1999</td>
<td>92</td>
<td>49 (18-68)*</td>
<td>HTx</td>
<td>ATG+P+A+C</td>
<td>2 (2.2%)</td>
<td>1 (1.1%)</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>10. Lederman et al, 1998</td>
<td>1137</td>
<td>47.1 (35-64)*</td>
<td>RTx</td>
<td>P+A (+C)</td>
<td>N/A</td>
<td>13 (1.1%)</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>11. Stelzner et al, 1997</td>
<td>1401</td>
<td>N/A</td>
<td>RTx</td>
<td>(P+A) or (P+C) or (P+A+C)</td>
<td>26 (1.9%)</td>
<td>21 (1.5%)</td>
<td>8 (38%)</td>
<td>8</td>
</tr>
<tr>
<td>12. Detry et al, 1996</td>
<td>143</td>
<td>54 (15-71)*</td>
<td>HTx</td>
<td>ATG+P+A+C</td>
<td>6 (4.2%)</td>
<td>4 (2.8%)</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>13. Soravia et al, 1995</td>
<td>2091</td>
<td>43 (10-61)*</td>
<td>RTx</td>
<td>(ALS+S+A) or (ALG+S+A+C)</td>
<td>N/A</td>
<td>9 (0.4%)</td>
<td>1 (8%)</td>
<td>10</td>
</tr>
<tr>
<td>14. McCune et al, 1992</td>
<td>1019</td>
<td>N/A</td>
<td>RTx</td>
<td>ATG+MP+C+A</td>
<td>4 (0.4%)</td>
<td>1 (0.1%)</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>15. Lao et al, 1988</td>
<td>325</td>
<td>N/A</td>
<td>RTx</td>
<td>(P+A) or (P+C)</td>
<td>3 (0.9%)</td>
<td>2 (0.6%)</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>16. Meyers et al, 1979</td>
<td>343</td>
<td>N/A</td>
<td>RTx</td>
<td>ATG+S+(A or Cp)</td>
<td>N/A</td>
<td>5 (1.5%)</td>
<td>N/A</td>
<td>8</td>
</tr>
<tr>
<td>17. Sawyer et al, 1978</td>
<td>113</td>
<td>Range from 16 to 63</td>
<td>RTx</td>
<td>N/A</td>
<td>7 (6.2%)</td>
<td>4 (3.5%)</td>
<td>4 (100%)</td>
<td>7</td>
</tr>
</tbody>
</table>

¹ Diverticulitis related, N/A non available
* mean (SD)
* mean (range)
# median (range)
^maximum score is 16 for non-comparative studies
LTx = Lungtransplantation, HTLx = Heart-Lung transplantation, RTx= Renal transplantation
ALS= anti-lymphocytic globulins, ATG= anti-thymocyte globulins, A= azathioprine
C= cyclosporine, Cp = cyclophosphamide, MMF= mycophenolate mofetil,
MP= methylprednisone, P= prednisone, R= rapamycin, S= steroids not further specified, T= tacrolimus
Table 2. Excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason of exclusion</th>
<th>N</th>
<th>Age</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leonardi et al, 2010</td>
<td>Case series describing the abdominal operations after lung transplantations: not focusing on diverticulitis</td>
<td>450</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Golda et al, 2010</td>
<td>No publication in journal, post organ transplant as part of immunosuppressed group, no control group</td>
<td>50</td>
<td>63.4*</td>
<td>There is no difference in morbidity-mortality for Hinchey III-IV diverticulitis</td>
</tr>
<tr>
<td>Benjamin et al, 2009</td>
<td>Only focussing on acute care surgical consultation within one year after renal transplantation, diverticulitis is not being specified</td>
<td>2340</td>
<td>N/A</td>
<td>Complicated diverticulitis after renal transplantation is rare</td>
</tr>
<tr>
<td>Catena et al, 2008</td>
<td>Focussing on polycystic kidney disease.</td>
<td>1611</td>
<td>N/A</td>
<td>Higher rate of colonic diverticular perforations.</td>
</tr>
<tr>
<td>Flanigan et al, 1988</td>
<td>Case series and literature review</td>
<td>587</td>
<td>N/A</td>
<td>Complicated cause rare</td>
</tr>
<tr>
<td>Starnes et al, 1985</td>
<td>Mixed population of post transplant patients and patients on dialysis</td>
<td>863</td>
<td>RTx</td>
<td>11 (1.3%)</td>
</tr>
<tr>
<td>Perkins et al, 1984</td>
<td>Mixed population including RTx.</td>
<td>90</td>
<td>N/A</td>
<td>Immunocompromised patients presented with either minimal or no symptoms and findings of diverticulitis.</td>
</tr>
<tr>
<td>Dominguez Fernandez et al, 1998</td>
<td>Only patient with RTx, cohort of ADPKD</td>
<td>46</td>
<td>50.5</td>
<td>No higher incidence of sigmoid perforation</td>
</tr>
<tr>
<td>Fenton et al, 1997</td>
<td>Case series</td>
<td>3</td>
<td>N/A</td>
<td>Incidence of 8.6% of diverticulitis,</td>
</tr>
<tr>
<td>Pirene et al, 1997</td>
<td>Complicated course not clearly stated</td>
<td>1530</td>
<td>36 *</td>
<td>Prophylactic colonic resection is advised</td>
</tr>
<tr>
<td>Beaver et al, 1996</td>
<td>Case series</td>
<td>4</td>
<td>N/A</td>
<td>Increased incidence of colonic perforation in</td>
</tr>
<tr>
<td>Abramson et al, 1991</td>
<td>Case series</td>
<td>2</td>
<td>N/A</td>
<td>Complicated diverticulitis should also be considered</td>
</tr>
<tr>
<td>Carson et al, 1978</td>
<td>Only perforations are discussed.</td>
<td>N/A</td>
<td>N/A</td>
<td>Perforated sigmoid diverticulitis is rare</td>
</tr>
<tr>
<td>Misra et al, 1973</td>
<td>Case series</td>
<td>6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* mean (± SD)
# median (range)
Heart transplantation

Five studies were included that analyzed colonic complications after heart transplantation, of which two studies had analyzed heart transplant recipients as a subgroup of a total group with both heart and lung transplant recipients.

Detry et al. report six cases (4.2%) of acute diverticulitis in their group of 143 heart transplant patients. Four patients (2.8%) developed complicated diverticulitis, with two diverticulitis-related perforations and two patients who developed abscesses. No deaths occurred (17). Mueller et al. found two cases (2.2%) of acute diverticulitis and one (1.1%) perforation within their group of 92 heart transplant recipients (18). Goldberg et al. found five cases (0.9%) of diverticulitis within their subgroup of 530 heart transplant recipients (19). Qasabian et al. found that within their subgroup of 639 heart transplant recipients, four patients (0.6%) developed severe inflammatory complications of diverticulitis, with three perforations and one abscess (20). Khan et al. report two (0.9%) cases of complicated diverticulitis with abscess formation in their subgroup of 233 heart transplant recipients (21).

Lung transplantation

Hoekstra et al. report five cases (4%) of complicated diverticulitis, all presenting with perforations, in a total of 125 post lung transplant patients. No diverticulitis related mortality was reported (22). Goldberg et al. found nine cases (2.1%) of diverticulitis
within their subgroup of 435 lung transplant recipients (19). Qasabian et al. found that within their subgroup of 248 lung transplant recipients, five patients (2.1%) presented with complicated diverticulitis, with three perforations and two abscesses (20). Khan et al. found no diverticulitis reviewing the charts of 35 lung transplant recipients (21). Paul et al. report three patients (1.4%) with diverticulitis and one case (0.5%) of complicated diverticulitis based upon perforation, within the reported 208 lung transplant recipients. One patient died due to the direct consequences of complicated diverticulitis (23). Maurer et al. reviewed 210 lung transplant recipients and found three cases (1.4%) of acute diverticulitis and six cases (2.9%) of complicated diverticulitis based upon perforations (24).

Heart-lung transplantation
Goldberg et al. found no cases of diverticulitis within their subgroup of heart-lung transplant recipients (19). Both Qasabian et al. and Paul et al. both found no cases of diverticulitis in their subgroups of 66 and two heart-lung recipients, respectively (20, 23).

Renal transplantation
Nine studies focusing on complicated diverticulitis after renal transplantation, containing a total of 8955 patients, are included in this study. Five studies reported separate data for acute diverticulitis; 40 acute cases were found in 4949 renal transplant patients (0.8%) with an incidence ranging from 0.4% to 6.2% (17, 25-27, 29). Incidence of complicated diverticulitis ranged from 0.1% to 3.5% in a total of 86 cases (17, 25-27, 29-34). Because of the high number of studies in renal transplant patients and their comparability, data were pooled. For complicated diverticulitis a pooled incidence of 1.0% (95% CI: 0.6% to 1.5%) was found (Figure 2). There was moderate evidence of heterogeneity among these studies ($I^2 = 39.8\%$; see also the funnel plot depicted in Figure 3).

Medication regimens
Table 1 shows the heterogeneity of the medications used for immunosuppressive therapy after transplantation. Most regimens consisted of prednisone together with azathioprine and/or cyclosporine after anti-thymocyte globulin induction.

Pooled data
Nine studies only included renal transplant patients. Pooled incidence of complicated diverticulitis in these patients was 1.0% (95% CI: 0.6 to 1.5%) with moderate evidence for heterogeneity ($I^2=37.8\%;$ see also the forest plot depicted in figure 2a).

Ten studies provided proportion of complicated diverticulitis, therefore only these studies were eligible for pooled analyses of proportion of complicated diverticulitis and incidence of acute diverticulitis. Pooled incidence of acute diverticulitis among these studies was 1.7% (95% CI: 1.0 to 2.7%) this was with moderate evidence for heterogeneity ($I^2=40.8\%$). Pooled proportion of complicated diverticulitis among patients with
Complicated diverticulitis in post-transplant patients, a systematic review.

Figure 2a. Forest plot of the incidence of complicated diverticulitis of the RTx studies. CI = confidence interval. Random effects model. $I^2 = 39.8\%$

Figure 2b. Forest plot of the incidence of acute diverticulitis within the included Tx studies. Pooled incidence of 1.7% (95% CI 1.0–2.7%) $I^2=40.8\%$
acute diverticulitis was 40.1% (95% CI: 32.2 to 49.7%). There was low heterogeneity among these studies ($I^2=0.01\%$; see also the forest plot depicted in figure 2b, and 2c).

**Excluded studies**

The excluded studies are summarized in Table 2 (28, 36, 37, 40-45, 48-50).

**DISCUSSION**

This systematic literature review showed an incidence of complicated diverticulitis in post-transplant patients ranging from 0.1% to 3.5%. Studies on renal transplantations could be pooled because of sufficient homogeneity. For complicated diverticulitis in renal transplantation patients a pooled incidence of 1.0% (95%CI: 0.6% to 1.5%) was found. For the incidence of acute diverticulitis only studies providing also the proportion of complicated diverticulitis were pooled. Pooled incidence of acute diverticulitis in these patients was 1.7% (95% CI: 1.0 to 2.7%) and pooled proportion of complicated diverticulitis in these patients was 40.1% (95% CI: 32.2 to 49.7%). The latter is important, because in non-immune compromised patients only 10-15% of the diverticulitis patients are presented with a complicated episode of diverticulitis (3).
In a large population-based study from the United States (685,390 diverticulitis discharges between 1991-2005), only 1.5% of patients with acute diverticulitis were found to have a perforation, and 9.6% were found to have an abscess (52). This means that within the group of post transplantation patients with acute diverticulitis a much higher percentage of primary complicated diverticulitis is seen compared to published data from an average population of non-transplant patients. Incidence of abscesses is underreported in our review, as most studies do not report abscesses.

Several studies have tried to identify possible risk factors for the development of diverticulitis or colonic complications. One of these possible risk factors is the use of immunosuppressive drugs. Hwang et al. have systematically reviewed all literature regarding the epidemiology and clinical course of diverticulitis in immunosuppressed patients (7). They have included a wide range of immunosuppressed patients due to corticosteroid therapy alone or corticosteroid therapy post transplantation. The endpoint of the systematic review of Hwang et al. was the prevalence of acute diverticulitis. They found that these patients had a higher rate of acute diverticulitis compared to a baseline population, with an incidence of 1% (7) compared to 0.6% in a large Swedish population based study (53). Their review presents a mixed population, in particular because of inclusion of patients on chronic corticosteroid therapy. No definition is documented in their review and the reviewed articles on what type, dose or duration of corticosteroid therapy these patients used. In our study incidence of acute diverticulitis in these patients was 1.7%.

The majority of studies included in the present review were of moderate methodological quality. In none of the studies statistical power calculations were performed. Another drawback of the available studies was the study design. All included studies lacked an adequate control group, namely a cohort of average risk healthy individuals of similar age. Therefore, there still remains uncertainty whether post-transplant patients with diverticulitis have an increased incidence of complicated and uncomplicated diverticulitis. In an effort to answer this question most studies compared their prevalence with previous published data concerning colonic screening in asymptomatic populations, as we did likewise, or with epidemiological data found in population-based registries. The interpretation of this systematic review might have been hampered by publication bias. Moreover, selective reporting can never be excluded. An important matter is the definition of complicated diverticulitis. In today’s studies a clear definition should be provided when discussing complicated or uncomplicated diverticulitis. Without a clear definition, the indication for an operation remains unclear. This is a possible selection bias, since it is unknown if patients with a phlegmone are operated. The indication for an operation could be also the fact that the patients are immunosuppressed.

Of the 17 studies included in our analyses only five provide a definition. Complicated diverticulitis is in these studies defined as perforated diverticulitis or with abscesses.
The exact mechanism by which patients receiving corticosteroids have an increased risk of diverticulitis is not known. Possible mechanisms include steroid-induced intestinal atrophy, depleted submucosal lymphoid patches and inhibition of the normal inflammatory reaction, causing bacterial invasion followed by perforation (42), as well as direct colon mucosal injury (54, 55).

The incidence of complicated and uncomplicated diverticulitis within the transplant patients appears higher that reported for an average population. If transplantation patients present with acute diverticulitis, a much higher proportion has a complicated disease course compared with published data from an average population. Therefore earlier operative intervention including elective resection after the first episode of diverticulitis in the immunosuppressed population could be made.
Complicated diverticulitis in post-transplant patients, a systematic review.

REFERENCES