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Oral Antibiotic Prophylaxis Can Influence the Inflammatory Response in Aortic Aneurysm Repair: Results of a Randomized Clinical Study

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Summary

The purpose of this prospective, randomized study was to evaluate the effect of oral ofloxacin prophylaxis on endotoxin/cytokine release in aortic aneurysm repair, in 25 patients with infrarenal aortic aneurysm at a University hospital. Outcome parameters included complications after operation; endotoxin and endotoxin neutralizing capacity. All patients had the standard perioperative antibiotic prophylaxis (2 g cefotiam). 12 patients randomly received oral ofloxacin prophylaxis (group 1) the day before the operation (200 mg/2x12h); 13 patients were controls (group 2). Data were analyzed by chi-square analysis, Mann-Whitney and Wilcoxon analysis. Ofloxacin had no effect on the occurrence of complications or on the peripheral endotoxin levels. Ofloxacin-treated patients showed increased endotoxin neutralizing capacity (ENC) 30 min after clamping compared to controls (15.8+-15 vs 262.8±709 p=0.005) and increased IL-6 levels preoperatively and 30 min after clamping. Patients with complications had significantly higher IL-6 levels early during the operation and postoperatively (30 min after clamping: 36.4±15.1 vs 18.8±11.9 pg/ml p=0.01; 2nd postoperative day: 768±688 vs 225±322 pg/ml p=0.005). Ofloxacin prophylaxis had no effect on procalcitonin, or neopterin plasma levels. Neither procalcitonin nor neopterin could detect patients with complicationsIL-6 plasma levels predicted the occurrence of complications in aortic aneurysm repair. Oral ofloxacin prophylaxis may influence the ENC and IL-6 plasma levels but had no effect on complications, endotoxin and other inflammatory mediators.

Key words: **ischemia-reperfusion, aortic aneurysm repair, endotoxin, endotoxin neutralizing capacity, IL-6, procalcitonin, neopterin, portal vein, ofloxacin, translocation.**

INTRODUCTION

Antibiotic prophylaxis in vascular surgery has been introduced to avoid prosthetic graft infection [1]. The combination of a broad-spectrum parenteral antibiotic with oral antibiotics in colorectal surgery is considered to reduce the postoperative complications, often caused by Gram-negative pathogens [2]. Gram-negative infections are associated with the release of endotoxin (LPS) from the disintegrating cell wall of Gram-negative pathogens [3] and cytokines [4]. Gut ischemia followed by translocation of endotoxin and bacteria may induce the systemic release of mediators [5]. Excessive cytokine production can lead to organ dysfunction, organ failure and death [6]. It is accepted that cytokines may be released in situations described by the term systemic inflammatory response syndrome (SIRS) without established infections [7]. This may be studied in elective abdominal aortic aneurysm (AAA) repair [8]

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where high levels of TNF-a originating from gut-associated macrophages may be activated by bowel manipulation, ischemia and/or translocated LPS [9]. Ischemia-reperfusion is a complex phenomenon, which may lead to a local and remote tissue injury and, in the case of an excessive immune response, to death [10]. This may be associated with a massive release of proinflammatory cytokines into the systemic circulation, contributing to the development of vascular injury by upregulation of adhesion molecules [11]. Such response may be sufficient to cause organ dysfunction without the presence of pathogens [12,13,14]. We have recently demonstrated in a clinical study in aortic aneurysm repair that endotoxin release is followed by an increase in pro- and anti-inflammatory cytokines [15]. Ofloxacin, a quinolone, with pronounced activity against Gram-negative pathogens [16] may lead to a complete elimination of Gram-negative bacilli in the bowel [17], not affecting the anaerobic microflora [18]. Ofloxacin may have an impact on the release of endotoxin and proinflammatory mediators. The purpose of this prospective, randomized study was to investigate the effects of additional oral ofloxacin prophylaxis on endotoxin and proinflammatory mediators in AAA repair.

PATIENTS AND METHODS

Twenty-five consecutive patients undergoing elective infrarenal AAA repair at a university department of surgery were included in this prospective, randomized study, approved by the Institutional Committee on Clinical Research. All patients received i.v. one dose (2g) of cefotetan. The study group (n=12) were given a dose of 200 mg ofloxacin in the morning and the evening of the preoperative day. The control group (n=13) nil. The aorta was always clamped below the renal arteries after routine systemic heparinization. Colonic mucosal pH or inferior mesenteric artery stump pressures were not recorded.

Plasma samples (venous) were obtained preoperatively (baseline), 30 minutes after incision, 30, 60, 90 and 120 minutes after clamping of the aorta, 4 and 8 hours after operation, and then the first, second and third postoperative day. The samples were kept cool, centrifuged and frozen within 30 minutes. Heparin was used as plasma anti-coagulant. Samples were centrifuged in endotoxin free tubes (Chromogenix, Germany) within 30 minutes and stored at -80°C until processing.

Endotoxin assay

We used the turbidimetric, kinetic LAL-test with internal standardization to measure endotoxin and endotoxin neutralizing capacity as described by Urbaschek *et al.* [19]. The sensitivity of the endotoxin test was 0.5 pg/ml.

IL-6 assay

IL-6 determinations were performed by a commercially available EASIA test (Medgenix Diagnostics, Fleurus, Belgium). The detection limit of the test is 2 ng/ml.

PCT assay

Procalcitonin was determined with LUMITEST PCT (Brahms Diagnostica, Berlin, Germany). Sensitivity of the assay was 0.3 ng/ml. The preliminary reference level for healthy human beings was 0.5 ng/ml. Concentrations above 0.5 ng/ml might indicate an inflammatory process.

Neopterin assay

For neopterin determination the ELITEST NEOPTERIN (Brahms Diagnostica, Berlin, Germany) was used. The reference level for healthy human beings was <= 10nmol/l.

Statistical analysis

The data are indicated as mean and standard deviation. The chi-square, Mann-Whitney and Wilcoxon-test were used for statistical analysis. Differences were considered significant if $p<0.05$.

RESULTS

Twenty-five patients (2 women, 23 men) with elective aortic aneurysm repair were randomized to receive ofloxacin (n=12) as additional oral prophylaxis the day before surgery (control group: nil n=13). There were three complications in group 1 and two complications in group 2. In group 1 one patient suffered from epileptic seizures. Two patients died: one patient died from severe pneumonia; the other patient died because of cardiovascular failure. In the control group one patient developed a lymph fistula but was discharged after further uneventful follow-up. The second patient had a complicated postoperative course with dissolution of the y-prosthesis due to severe thrombosis and consecutive renal failure, which made a dialysis necessary. After a prolonged hospitalization the patient was discharged.

The patients (Groups 1 and 2) did not differ in age, sex, operation time and clamping time of the aorta, and routine laboratory data. The mean operation time was 288.7±24 minutes for y-prosthesis of the aorta and 133.8±13 minutes for a Dacron graft. Mean clamping time of the aorta was 48.8±10.8

minutes and 45.7±2 minutes respectively. Leukocytes increased significantly on the day of operation ($p<0.05$) and on the first ($p<0.01$) and second postoperative days ($p<0.05$). Thrombocytes decreased significantly on the day of operation and the first postoperative day ($p<0.01$). The hemoglobin levels decreased significantly intra-operatively, on the day of operation and remained significantly lower than preoperative levels on the first, second and third postoperative days ($p<0.001$). There was a significant decrease in the hematocrit from preoperative levels on the second postoperative day ($p<0.001$) and on the third postoperative day ($p<0.05$). Temperature decreased intra-operatively ($p<0.001$) and increased significantly on the day of operation and the first postoperative day ($p<0.001$).

Endotoxin was not detected preoperatively in the patients. The maximum endotoxin level was measured 60 minutes after clamping of the aorta (3±2.9 pg/ml). Endotoxin levels increased significantly 30 minutes after incision and remained significantly elevated when compared to pre-operative levels, until 4 hours after operation ($p<0.01$). The endotoxin plasma levels on the first, second and third postoperative days did not reach statistical significance when compared to preoperative levels. (*Figure 1*) There was no difference in endotoxin levels in patients treated with ofloxacin and controls. (*Figure 2*) Patients with and without complications had a similar pattern of endotoxin plasma levels. Sixty minutes after aortic clamping plasma endotoxin was higher in patients without complications without reaching statistical difference.

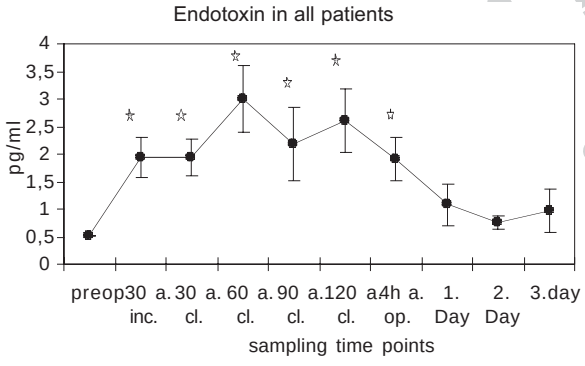

FIGURE 1 - Endotoxin plasma levels in all patients (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): endotoxin is significantly * increased 30 minutes after incision ($p<0.05$), 30, 60, 90 and 120 minutes after clamping ($p<0.05$) and 4 hours after operation ($p<0.05$)

The endotoxin neutralizing capacity declined significantly from the preoperative baseline measurement at 60, 90, 120 minutes after clamping and 4 hours after operation ($p<0.05$). It increased to maximum at the first postoperative day (357.6±217.64) and remained at preoperative index levels on day 2 (96±29.48) and day 3 (142.46±49.42) after surgery. (*Figure 3*) Endotoxin neutralizing capacity levels were almost significantly elevated in preoperative ofloxacin-treated patients when compared to controls ($p=0.0972$). Ofloxacin-treated patients had significantly elevated endotoxin neutralizing capacity index at 30 minutes after clamping compared to controls (15.8±15 vs 262.8±709.2 $p=0.0055$). Endotoxin neutralizing capacity levels in ofloxacin-treated patients were almost significantly elevated 30 minutes after incision ($p=0.0881$), 120 minutes after clamping ($p=0.0662$) and on the second postoperative day ($p=0.0849$). (*Figure 4*) There was no difference in endotoxin neutralizing capacity in patients who had complications and in patients who had an uneventful recovery. (*Figure 5*)

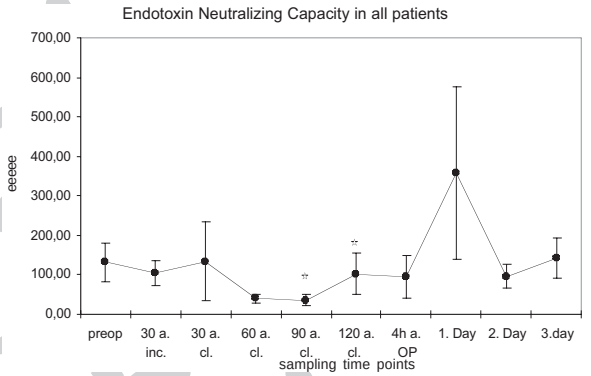

FIGURE 2 - Endotoxin plasma levels in patients with and without oral ofloxacin (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): there is no difference in plasma endotoxin levels of patients treated with or without ofloxacin.

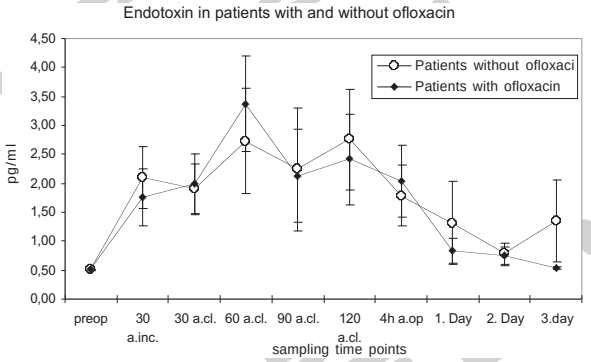

FIGURE 3 - Endotoxin neutralizing capacity (ENC) in all patients (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): ENC is significantly * decreased 90 minutes ($p<0.05$) and 120 minutes after clamping ($p<0.05$), 4 hours after operation ($p<0.05$), and almost significantly 60 minutes after clamping ($p=0.056$).

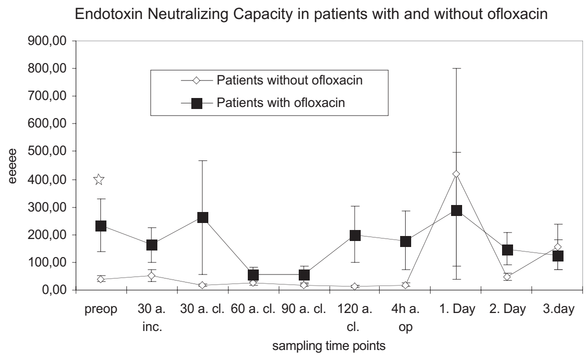

FIGURE 4 - Endotoxin neutralizing capacity (ENC) in patients with and without oral ofloxacin (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): ENC is significantly * increased in ofloxacin-treated patients preoperatively (p<0.05), and almost significantly elevated 30 minutes after incision (p=0.08), 120 minutes after clamping (p=0.06), and the 2. day (p=0.08)

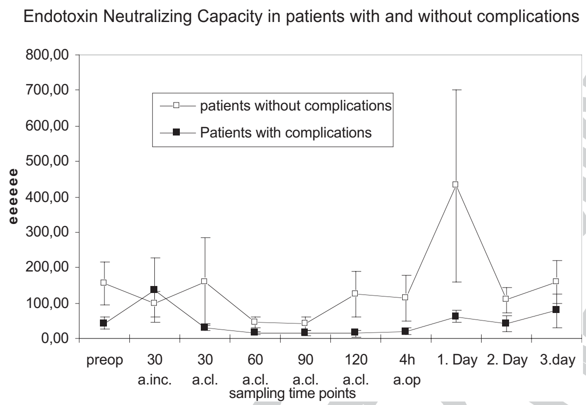

FIGURE 5 - Endotoxin neutralizing capacity (ENC) in patients with and without complications (preop=preoperative, a.inc. = after incision, a.cl. = after clamping): no significant difference detected.

Interleukin-6 (IL-6) concentrations decreased significantly 30 and 60 minutes after clamping when compared to preoperative levels (p<0.05). There was a significant increase observed at 60, 90, 120 minutes after clamping, and 4 hours after operation which remained significantly elevated until day 3 after operation (p<0.001). Patients who received ofloxacin had almost significantly elevated IL-6 levels preoperatively when compared to controls (p=0.0866). Thirty minutes after incision IL-6 levels in ofloxacin-treated patients were significantly higher than untreated controls (p<0.05). (*Figure 6*) Patients with complications had significantly higher IL-6 plasma levels 30, 60, 90 minutes after clamping and on the second postoperative day (p<0.05). Plasma IL-6 levels were not quite significantly elevated 120 minutes after clamping and on day 3 after operation. (*Figure 7*)

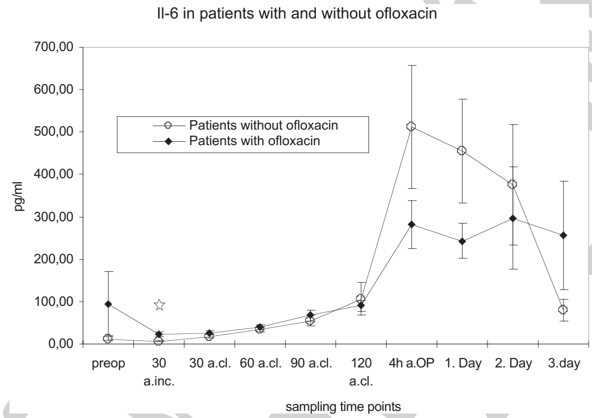

FIGURE 6 - Interleukin-6 (IL-6) plasma concentration in patients with and without oral ofloxacin (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): IL-6 levels are preoperatively (p=0.08) almost significantly and 30 minutes after incision (p=0.01) significantly * elevated compared to controls *.

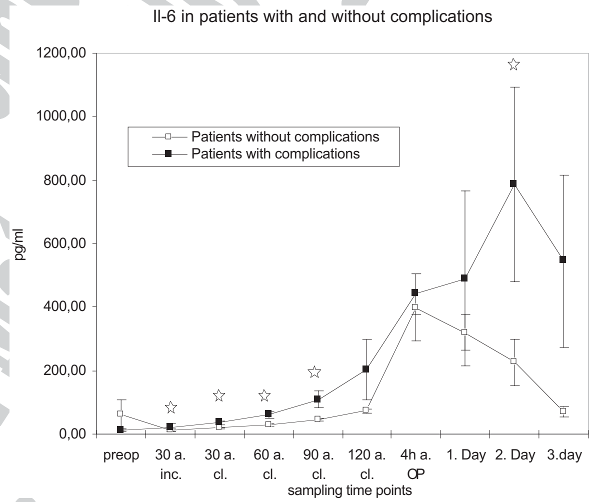

FIGURE 7 - Interleukin-6 (IL-6) plasma concentration in patients with and without complications (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): IL-6 plasma levels are significantly * different in patients with postoperative complications early after incision (30 minutes after incision p<0.05; 30, 60, 90 minutes after clamping of the aorta and on day 2 p<0.05).

Procalcitonin levels did not remain at their normal preoperative level during the perioperative period. At the first postoperative day procalcitonin increased significantly (0.27±0.03 vs 1.93±0.8 ng/ml) and remained elevated on the second and third postoperative day. Treatment and control groups demonstrated no difference in **PCT (AUTHORS, DEFINE PCT)** levels. Patients with complications tended to have higher PCT levels but maximum PCT levels on the second postoperative day were not significantly different when compared

to patients without complications (6.16±7.76 vs 0.87±1.17 ng/ml p=0.06).

Neopterin plasma levels declined at 30 minutes after incision (7.5±4.9 nmol/l) compared to preoperative levels (9.7±6.8 nmol/l). Maximum levels of neopterin were measured on the third postoperative day (15.72±2.29 nmol/l). There was no difference in plasma neopterin levels either in patients who were treated with ofloxacin compared to controls or in patients with and without complications.

DISCUSSION

Endotoxemia is a common finding after vascular operations [20]. Cohen *et al.* suggest that increased intestinal permeability is associated with supraceliac colic clamping [21]. Aortic aneurysm repair has been associated with ischemia of the bowel [22] and endotoxin induces activation of cellular and humoral mediators and endotoxin core antibodies [23]. We have recently demonstrated that there is a concomitant release of inflammatory and anti-inflammatory mediators in aortic aneurysm repair which may be induced by endotoxin release from bacterial wall of Gram-negative pathogens in the bowel [13]. Studies on the pharmacokinetics of ofloxacin reveal a high fecal concentration which persists for several days [24] and ofloxacin may cause a selective reduction in the normal microflora, mainly aerobic Gram-negative bacteria [25]. Oral antibiotic prophylaxis is frequently used for bowel surgery and recently it has been suggested that oral prophylaxis with ofloxacin in general surgery may be as effective as intravenous prophylaxis [26].

The hypothesis of the present study was that additional oral antibiotic prophylaxis in aortic aneurysm repair might lead to less endotoxin release and a reduced activation of the inflammatory system. This may have an effect on the clinical outcome.

Patients were randomized to receive either 2x200mg ofloxacin orally the day before AAA repair or to be in the control group without oral antibiotic prophylaxis. Endotoxin was detected early in the operative course in all patients and remained elevated postoperatively. The increase in endotoxin plasma concentration was correlated with a concomitant decrease in endotoxin neutralizing capacity. This is in agreement with recently published findings [13].

Antibiotics may have a distinctive effect on endotoxin release [27,28]. Orally administered nonadsorbable antibiotics prevented endotoxemia in primates following intestinal ischemia [29]. Altering the gut contents in a rat model of hepatic failure and coma after liver resection reduced the level of endotoxemia [30]. In this study, however, patients treated with ofloxacin did not differ in plasma endotoxin levels; however, there was a significant difference in endotoxin plasma neutralization. *In-vitro* studies revealed that ofloxacin might not reduce TNF-alpha production from LPS-stimulated monocytes *in vitro* [31]. Several factors, which were not determined in this study, may have influenced the determination of endotoxin in plasma**.** We did not determine intramucosal pH in these patients, which may influence the concentration of endotoxin, TNF, and IL-6 in elective aortic aneurysm patients [32]. Furthermore, manipulation of the bowel [33] may have a stronger influence than the neutralization of the Gram-negative pathogens by ofloxacin. In other studies it is demonstrated that endotoxin is released in low concentrations and may escape detection by the limulus assay [34]. Subinhibitory concentrations of ofloxacin are known to enhance the phagocytic killing rate [35], which may increase the plasma endotoxin level, whereas diminished bactericidal activity of ofloxacin is associated with the lowest release of endotoxin [36]. This is in contrast to *in-vitro* data, which elucidated that LPS is released as long as *Escherichia coli* remains structurally intact and is enhanced when the bacterial biomass increases [37]. Antibiotic-induced endotoxin release in quinolones is influenced considerably by dosage and pharmacodynamics [38]. Ofloxacin may not reduce sufficiently the amount of anaerobic pathogens in the bowel [39] and products from anaerobes may induce limulus amebocyte lysate activation. We observed a significant increase in the endotoxin neutralizing capacity and almost significantly increased levels of IL-6 preoperatively in ofloxacin-treated patients, which suggests that ofloxacin may influence the immune response. The increased endotoxin neutralizing capacity has been observed in surgical intensive care patients treated with ciprofloxacin and imipenem [40]. There are no other reports with regard to the effect of ofloxacin and endotoxin neutralizing capacity available. The situation with decontamination of the gut remains inconclusive even when nonabsorbable antibiotics (polymyxin B, neomycin) are used [41,42].

We demonstrated endotoxin in a branch of the mesenteric vein during the operation but before clamping. It may be that endotoxin release is more affected by local microcirculation disturbance induced at the beginning of the operation than by the effect of clamping. Endotoxin and proinflammatory mediators have been detected in the portal vein by several investigators [43]. Our findings of an early increase in IL-6 levels in the mesenteric vein are in agreement with these reports. The significantly increased IL-6 levels in the mesenteric vein compared to systemic levels support the notion that IL-6 may be locally released by activated gut macrophages. Oxidative stress may have triggered

this release of cytokines and induced the inflammation [44]. Endotoxin may be neutralized by several factors, e.g., plasma proteins, lipids, which may affect endotoxin measurement and the interpretation of results. Other mediators may be easier to determine and may help to provide additional information on the effect of ofloxacin treatment. IL-6, procalcitonin and neopterin, which are known to be increased in SIRS and sepsis, [45, 46, 47] were not affected by ofloxacin treatment.

The identification of patients at risk for complications may have definite clinical benefit. There were 5 patients with complications (20%) recorded in the study; patients treated additionally with ofloxacin did not experience significantly fewer complications. The efficacy of antibiotic prophylaxis has been recently demonstrated in a multicenter trial [48].

While endotoxin plasma levels in thoracoabdominal aortic aneurysm repair are correlated with CD11b expression, a marker of neutrophil activation, which predicts postoperative complications, [49] low concentrations of endotoxin were not associated with complications in this study.

In a recent European multicenter study, surgical intensive care patients with complicated outcome showed significantly decreased endotoxin neutralizing capacity of the plasma compared to controls ;[50,50] however, this study did not detect any differences between patients with and without complications, although patients treated with ofloxacin had increased endotoxin neutralizing capacity shortly after clamping of the aorta. IL-6 increased significantly early during the aortic aneurysm repair in patients with complicated follow-up. The increased IL-6 levels in the splanchnic vessel system suggest that the gut and the local proinflammatory cytokine production may have a major impact on the development of septic complications. Local cytokine production and immune compartmentalization are major factors in the development of intra-abdominal sepsis [51].[51]

Procalcitonin levels did not predict complications in patients in this study. In patients with neuroendocrine tumors high levels of these peptides were detected, indicating that factors other than systemic inflammatory response syndrome (SIRS) alone may influence PCT release [46]. Despite reports that procalcitonin may be an appropriate marker for indicating the early development of severe noninfective SIRS [52] the predictive value of PCT for a forthcoming multiple organ failure remains to be established [53]. Neopterin, a marker of macrophage activation [54] may discriminate between survivors and non-survivors, and between septic and non-septic patients,[55] which are increased in burn patients [56] and may be a predictor of shock [57]. In a hemorrhagic traumatic shock model LPS induced a systemic release of neopterin in septic animals [58]. Most of these studies investigated the release of neopterin in sepsis and severe SIRS. However, in this clinical model of moderate ischemia-reperfusion neopterin failed to demonstrate a difference in clinical complications. However, a significant increase of neopterin may have occurred later as in burn patients three days post-burn [59].

CONCLUSION

In conclusion, in abdominal aortic aneurysm repair there is an increase of endotoxin-induced proinflammatory mediators. Ofloxacin may have reduced the amount of Gram-negative pathogens but this may have been outweighed by other factors leading to an activation of the limulus amebocyte lysate test system. Ofloxacin treatment increased the endotoxin neutralizing capacity, but did not affect the levels of proinflammatory mediators with the exception of IL-6 levels, at least in this study. Complications were preceded by an early, significant increase of IL-6, which may be released from local gut-activated macrophages. Other mediators, e.g., procalcitonin, neopterin, were not sensitive enough to predict adverse outcome.

REFERENCES

[1] Holzheimer RG. Antibiotic prophylaxis. In: Holzheimer RG, Mannick JA (eds.). Surgical Treatment - Evidence-based and problem-oriented. Zuckschwerdt Verlag, München Bern Wien New York 2001:722-731.

[2] Nichols RL, Holmes JW. Prophylaxis in bowel surgery. Curr Clin Top Infect Dis 1995;15:76-96.

[3] Hinshaw LB. Pathophysiology of endotoxin action: an overview. In: Novotny A, Spitzer JJ, Ziegler EJ (eds.). Cellular and molecular aspects of endotoxin reactions. Elsevier BV 1990: 419 - 426.

[4] Cannon JG, Tomkins RG, Gelfand JA, *et al*. Circulating Interleukin-1 and Tumor Necrosis Factor in septic shock and experimental endotoxin fever. J Infect Dis 1990; 161: 790-84.

[5] Van Deventer SJH, Cate JW, Tytgat GNJ. Intestinal endotoxemia. Gastroenterology 1988; 94: 825-831.

[6] Knaus WA, Wagner DP. MSOF:epidemiology and prognosis. In: Pinsky MR, Matuschak JM (eds). Critical care clinics. Multiple systems organ failure. WB Saunders. Philadelphia 1989: 221-232.

[7] Cavaillon JM, Haeffner-Cavaillon N. Cytokines and inflammation. Rev Prat 1993; 43: 547-552.

[8] Farkas JC, Calvo-Verjat N, Laurian C, *et al*. Acute colorectal ischemia after aortic surgery: pathophysiology and prognostic criteria. Ann Vasc Surg 1991; 6: 1-8.

[9] Cabie A, Farkas JC, Fitting C, *et al*. High levels of portal TNF-alpha during abdominal aortic surgery in man. Cytokine 1993 ; 5 (5): 448-453.

[10] Grace PA. Ischaemia-reperfusion injury. Br J Surg 1994; 81: 637-647.

[11] Ward PA. Ischemia, reperfusion and organ dysfunction: biochemical and cellular events. J Vasc Surg 1993 ; 18: 111.

[12] Goris RJA, te Boekhorst TPA, Nuytinck JKS, Gimbrere

JSF. Multiple organ failure: generalized autodestructive inflammation? Arch Surg 1985; 120: 1109-1115.

[13] Dinarello CA, Mier JW. Current concepts - lymphokines. New Engl J Med 1987; 317: 940-945.

[14] Deitch EA. Multiple organ failure: pathophysiology and potential future therapy. Ann Surg 1992; 216: 117-134.

[15] Holzheimer RG, Gross J, Schein M. Pro- and anti-inflammatory cytokine-response in abdominal aortic aneurysm repair: A clinical model of ischemia-reperfusion. Shock 1999; 11: 305-310.

[16] Edlund C, Kager L, Malmborg AS, Sjostedt S, Nord CE. Effect of ofloxacin and gastrointestinal microflora in patients undergoing gastric surgery. Eur J Clin Microbiol Infect Dis 1988; 7: 135-143.

[17] Leigh DA, Walsh B, Harris K, Hancock P, Travers G. Pharmacokinetics of ofloxacin and the effect on the faecal flora of healthy volunteers. J Antimicrob Chemother 1988; 22, Suppl C, 115-125.

[18] Nord CE. Effect of new quinolones on the human gastrointestinal microflora. Rev Infect Dis 1988;10 Suppl1: S193-S196.

[19] Urbaschek R, Becker KP. [Detection of endotoxin in plasma: specificity and value for development and prognosis of infection] Endotoxinnachweis im Plasma: Spezifitat und Aussagekraft fur Entwicklung und Prognose einer Sepsis. Infusionsther Transfusionsmed 1993; 20 Suppl 1: 16-19.

[20] Roumen RM, Frieling JT, van Tits HW, van der Vliet JA, Goris RJ. Endotoxemia after major vascular operations. J Vasc Surg 1993; 18: 853-857.

[21] Cohen JR, Sardari F, Paul J, *et al*. Increased intestinal permeability: implications for thoracoabdominal aneurysm repair. Ann Vasc Surg 1992; 6: 433-437.

[22] Soong CV, Blair PH, Halliday MI, *et al*. Bowel ischemia and organ impairment in elective abdominal aortic aneurysm. Br J Surg 1994; 81: 965-968.

[23] Soong CV, Halliday MI, Barclay GR, Hood JM, Rowlands BJ, Barros D'SA AA. Intramucosal acidosis and systemic host responses in abdominal aortic aneurysm surgery. Crit Care Med 1997; 25: 1472-1479.

[24] Leigh DA, Walsh B, Harris K, Hancock P, Travers G. Pharmocokinetics of ofloxacin and the effect on the faecal flora of healthy volunteers. J Antimicrob Chemother 1988; 22, Suppl C: 115-125.

[25] Edlund C, Sjostedt S, Nord CE. Comparative effects of levofloxacin and ofloxacin on the normal oral and intestinal microflora. Scand J Infect Dis 1997; 29 (4): 383-386.

[26] Schwarz M, Isenmann R, Thomsen J, Gaus W, Beger HG. Efficacy of oral ofloxacin for single-dose perioperative prophylaxis in general surgery--a controlled randomized clinical study. Langenbecks Arch Surg 2001; 386 (6): 397-401.

[27] Periti P, Mazzei T. Antibiotic-induced release of bacterial cell wall components in the pathogenesis of sepsis and septic shock: a review. J Chemother 1998; 10 (6): 427-448.

[28] Holzheimer RG. Antibiotic induced endotoxin release and clinical sepsis: a review. J Chemother 1999; 13 (Spec Issue 1): 159-172.

[29] Gathiram P, Wells MT, Brock-Utne JG, Wessels BC, Gaffin SL. Oral administered nonadsorbable antibiotics prevent endotoxemia in primates following intestinal ischemia. J Surg Res 1988; 45 (2): 187-193.

[30] van Leeuwen PA, Hong RW, Rounds JD, Rodrick ML, Wilmore D. Hepatic failure and coma after liver resection is reversed by manipulation of gut contents: the role of endotoxin. Surgery 1991; 110 (2): 169-174.

[31] Iino Y, Toriyama M, Kudo K, Natori Y, You A. Erythromycin inhibition of lipopolysaccharide-stimulated tumor necrosis factor alpha production by human monocytes in vitro. Ann Otol Rhinol Laryngol Suppl 1992; 157: 16-20.

[32] Soong CV, Blair PH, Halliday MI, *et al*. Endotoxemia, the generation of the cytokines and their relationship to intramucosal acidosis of the sigmoid colon in elective abdominal aortic aneurysm repair. Eur J Vasc Surg 1993; 7 (5): 534-539.

[33] Lau LL, Halliday MI, Lee B, Hannon RJ, Gardiner KR, Soong CV. Intestinal manipulation during elective aortic aneurysm surgery leads to portal endotoxemia and mucosal barrier dysfunction. Eur J Vasc Endovasc Surg 2000; 19 (6): 619-624.

[34] Lamp KC, Rybak MJ, McGrath BJ, Summers KK. Influence of antibiotic and E5 monoclonal immunoglobulin M interactions on endotoxin release from *Escherichia coli* and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 1996; 40: 247-252.

[35] Pulverer G, Peters G. Investigations on ofloxacin antibacterial activity and influence on the immune system. Infection 1986;14 Suppl 4: S245-S247.

[36] Lamp KC, Rybak MJ, McGrath BJ, Summers KK. Influence of antibiotic and E5 monoclonal immunoglobulin M interactions on endotoxin release from *Escherichia coli* and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 1996; 40 (1): 247-252.

[37] van den Berg C, de Neeling AJ, Schot CS, Hustinx WN, Wemer J, de Wildt DJ. Delayed antibiotic-induced lysis of Escherichia coli in vitro is correlated with enhancement of LPS release. Scand J Infect Dis 1992; 24 (5): 619-627.

[38] Nitsche D, Schulze C, Oesser S, Dalhoff A, Sack M. Impact of different classes antimicrobial agents on plasma endotoxin activity. Arch Surg 1996; 131 (2): 192-199.

[39] Nord CE. Effect of new quinolones on the human gastrointestinal microflora. Rev Infect Dis 1988; 10 Suppl 1: S193-S196.

[40] Holzheimer RG, Hirte JF, Reith B, *et al*. Different endotoxin release and IL-6 plasma levels after antibiotic administration in surgical intensive care patients. J Endotoxin Res 1996; 3(3): 261-267.

[41] Bouter H, Schippers EF, Luelmo SA, *et al*. No effect of preoperative selective gut decontamination on endotoxemia and cytokine activation during cardiopulmonary bypass: a randomized, placebo-controlled study. Crit Care Med 2002; 30 (1): 38-43.

[42] Martinez-Pellus AE, Merino P, Bru M, *et al*. Endogenous endotoxemia of intestinal origin during cardiopulmonary bypass. Role of type of flow and protective effect of selective digestive decontamination. Intensive Care Med 1997; 23 (12): 1251-1257.

[43] Baigrie RJ, Lamont PM, Whiting S, Morris PJ. Portal endotoxin and cytokine responses during abdominal aortic surgery. Br J Surg 1993; 166: 248-251.

[44] Fan J, Marshall JC, Jiminez M, Shek PN, Zagorski J, Rotstein OD. Hemorrhagic shock primes for increased expression of cytokine-induced neutrophil chemoattractant in the lung: role in pulmonary inflammation following lipopolysaccharide. J Immunol 1998; 161: 440-447.

[45] Holzheimer RG, Molloy RG, Mendez MV, *et al*. Multiple organ failure may be influenced by macrophage hypoactivation as well as hyperactivation - importance of the double hit. Eur J Surg 1995;161: 795-803.

[46] Snider RH, Nylen ES, Becker KL. Procalcitonin and its component peptides in systemic inflammation: immunochemical characteristics. J Investig Med 1997; 45: 552-560.

[47] Pacher R, Redl H, Frass M, Petzl DH, Schuster E, Woloszzuk W. Relationship between neopterin and granulocyte elastase plasma levels and the severity of multiple organ failure. Crit Care Med 1989; 17: 221-226.

[48] Pratesi C, Russo D, Dorigo W, Chiti E. Antibiotic prophylaxis in clean surgery: Vascular surgery. J Chemother 1999;13 (spec issue 1): 123-128.

[49] Foulds S, Cheshire NJ, Schachter M, Wolfe JH, Mansfield AO. Endotoxin related early neutrophil activation is associated with outcome after thoracoabdominal aortic

aneurysm repair. Br J Surg 1997; 84: 172-177.

[50] Holzheimer RG, Capel P, Cavaillon JM, *et al*. Immunological surrogate parameters in a prognostic model for multi-organ failure and death. Eur J Med Res 2000; 5 (7): 283-294.

[51] Holzheimer RG, Schein M, Wittmann DH: Inflammatory response in peritoneal exudate and plasma of patients undergoing planned relaparotomy for severe secondary peritonitis. Arch Surg 1995, 130: 1314-1320.

[52] Hensel M, Volk T, Docke WD, *et al*. Hyperprocalcitonemia in patients with noninfectious SIRS and pulmonary dysfunction associated with cardiopulmonary bypass. Anaesthesiology 1998; 89: 93-104.

[53] Mimoz O, Benoist JF, Edouard AR, Assicot M, Bohuon C, Samii K. Procalcitonin and C-reactive protein during the early postraumatic systemic inflammatory response syndrome. Intensive Care Med 1998; 24: 185-188.

[54] Strohmaier W, Redl H, Schlag G, Inthorn D. D-erythro-neopterin plasma levels in intensive care patients with and without septic complications. Crit Care Med 1987; 15: 757-760.

[55] Pacher R, Redl H, Frass M, Petzl DH, Schuster E, Woluszczuk W. Relationship between neopterin and granulocyte elastase plasma levels and the severity of multiple organ failure. Crit Care Med 1989; 17: 221-226.

[56] Burleson DG, Johnson A, Salin M, Mason AD, Pruitt BA. Identification of neopterin as a potential indicator of infection in burned patients. Proc Soc Exp Biol Med 1992; 199: 305-310.

[57] Delogu G, Casula MA, Mancini P, Tellan G, Signore L. Serum neopterin and soluble interleukin-2 receptor for prediction of a shock state in gram-negative sepsis. J Crit Care 1995; 10: 64-71.

[58] Strohmaier W, Werner ER, Wachter H, Redl H, Schlag G. Pteridine and nitrite/nitrate formation in experimental septic and traumatic shock. Shock 1996; 6: 254-258.

[59] Yao YM, Yu K, Wang YP, Tian HM, Sheng ZY. Elevated serum neopterin level: its relation to endotoxemia and sepsis in patients with major burns. Eur J Clin Invest 1996; 26: 224-230.