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Postimplantation Syndrome after Endovascular Aneurysm Repair

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<http://dx.doi.org/10.5772/intechopen.77392>

Abstract

Endovascular aneurysm repair is associated, in a significant proportion of patients, to a systemic inflammatory response denominated postimplantation syndrome (PIS). PIS is characterized by fatigue, fever, and a rise in inflammatory biomarkers after the operation. However, the exact definition is still a matter of debate. There are several proposed definitions for PIS in the literature resulting in significant variability of PIS incidence (ranging from 2% to 100%). The etiology of PIS is not entirely clear. Endograft composition, aortic thrombus, intestinal bacterial translocation, and contrast media may contribute to PIS but the first seems to be the most important determinant. This clinical entity may have clinical consequences in length of hospital stay, readmissions, renal function, cardiovascular events, endoleak rate, and quality of life, but current data are insufficient for definitive conclusions. Despite of absence of established treatment for PIS, non-steroid and steroid anti-inflammatory drugs are currently advocated when clinical suspicion arises. Prevention may be achieved with perioperative administration of a steroid drug. Since it may have adverse effects, further knowledge of the real incidence of PIS and its clinical consequences is imperative.

Keywords: inflammation, inflammatory response syndrome, systemic, foreign-body reaction, aneurysm, aortic aneurysm, abdominal, aortic aneurysm, thoracic, endovascular procedures

1. Introduction

Endovascular aneurysm repair is associated, in a significant proportion of cases, to a systemic inflammatory response that was denominated Postimplantation syndrome (PIS) [1]. PIS was

first described in 1999 by Velazquez et al. [2] as a syndrome of fever and leukocytosis after aortic stent-graft implantation. It was incidentally noted in prior clinical studies on EVAR, but the exact origin is unknown. The authors suggested that these manifestations, comprising fatigue or other constitutional (flu-like) symptoms, fever and laboratory findings of inflammation, are a reproducible phenomenon specific to the nature of this procedure, rather than related to postoperative infections [2].

In fact, experimental studies in animals had suggested a local peri-aortic inflammatory response to endovascular exclusion of aneurysms. For example, in a study in sheep that underwent to endovascular implantation of heparin-coated Dacron-covered grafts, the macroscopic examination of the arterial wall revealed significant inflammatory peri-graft response with vascular thickening and adhesions around the grafts. Microscopic examination revealed a severe foreign-body response [3].

Several publications addressing the issue have been published since 1999. However, there is still no consensus over the definition for the syndrome, its real incidence, associated factors, consequences, treatment, and eventually prophylactic therapy.

2. Definition and incidence

PIS is defined as fatigue and fever associated to a rise in inflammatory biomarkers. Which markers should be used and their cutoff values is still a matter of debate. There are several proposed combinations of fever, leukocytosis, and elevated C-reactive protein (CRP) used as definition for PIS in the literature. Some authors defined PIS as the presence of fever coinciding with an elevated serum CRP level, whereas the majority of them adapted the systemic inflammatory response syndrome (SIRS) criteria and defined PIS as the presence of fever combined with leukocytosis [1, 2, 4–11].

Arnaoutoglou et al. [10] defined PIS as the presence of fever ($>38^{\circ}\text{C}$) and leukocytosis ($>12,000/\mu\text{L}$). However, they verified that hs-CRP values were strongly related to the presence of PIS and also emerged as an important predictor of the 30 day-outcome. Therefore, they concluded that hs-CRP probably is a better marker to inflammatory response. The reported incidence of PIS in the literature varies widely, and the lack of a universally accepted definition may be responsible for this. Reported incidence ranges from 2 to 100% (**Table 1**).

Blum et al. [12], analyzed prospectively the clinical outcome after EVAR in 154 patients. All were treated with polyester-covered nitinol endograft and 87 patients (56%) developed fever (temperature, $38.0\text{--}39.7^{\circ}\text{C}$), that lasted for 4–10 days, without evidence of bacteremia or graft infection. All patients showed leukocytosis (range from 9.800 to $29,500/\mu\text{L}$) in laboratory tests and an elevation of C-reactive protein concentrations (range from 4 to 34.1 mg/dL) [12].

Two years after, Velazquez et al. [2] developed the first study specifically aimed at describing and understanding the postimplantation syndrome, characterized by fever and leukocytosis

| Authors, Publication, Journal | Year of | Study design | Number of included patients | Fever | Leukocyte count | CRP | Incidence of PIS |
|---|---------|---------------------------------------|-----------------------------|---------|-----------------|------------|------------------|
| Unclear definition | | | | | | | |
| Blum et al., 1997, New England Journal of Medicine (12) | | Prospective | 154 | ns | ns | ns | 56% |
| Chang et al., 2014, Journal of Vascular Surgery(14) | | Prospective | 38 | ns | ns | ns | 47% |
| Georgiadis et al., 2011, Journal of Vascular Surgery (15) | | Prospective | 77 | ns | ns | ns | 36,4% |
| Mazzaccaro et al., 2016, Annals Vascular Surgery (16) | | Retrospective | 10 | ns | ns | ns | 30% |
| Melissano et al., 2015, Journal of Vascular Surgery (17) | | Retrospective | 42 | ns | ns | ns | 2% |
| Definition with leukocytosis and fever | | | | | | | |
| Amaoutoglou et al., 2011, Interact Cardiovasc Thorac Surg (4) | | Prospective | 162 | >38°C | >12.000/ml | - | 30.2% |
| Dostluoglu et al., 2014, Journal Vascular Surgery (6)*** | | Retrospective | 79 | >37.8°C | >10.000/ml * | - | 23% |
| Nano et al., 2014, Annals Vascular Surgery (8)*** | | Retrospective | 118 | >38°C | >12.000//ml | - | 20,3% |
| Kakialis et al., 2014, Journal Vascular Surgery (18) | | Retrospective | 87 | >38°C | >12.000//ml | - | 39% |
| Amaoutoglou et al., 2014, European Journal Cardiovascular Surgery (10) | | Prospective | 214 | >38°C | >12.000//ml | - | 36% |
| Sartipy et al., 2015, Vasc Endovasc Surgery (19) | | Prospective | 45 | >38°C | >12.000//ml | - | 28% |
| Kwon et al., 2016, Medicine (20) | | Retrospective | 204 | >38°C | >12.000//ml | - | 31,4% |
| Amaoutoglou et al., 2016, Journal Vascular Surgery (21) | | Prospective | 182 | >38°C | >12.000//ml | - | 35.7% |
| Definition with fever and CRP | | | | | | | |
| Voûte et al., 2012, Journal Vascular Surgery (5) | | Retrospective | 149 | >38°C | - | > 10 mg/L | 38.9% |
| Goria et al., 2015, European Journal of Cardio-Thoracic Surgery (22)*** | | Retrospective | 133 | >38°C | >12.000//ml | > 100 mg/L | 15,8% |
| SIRS criteria with CRP instead of leukocyte count | | | | | | | |
| De la Motte et al., 2014, Annals of Surgery (7) | | Prospective, randomized, double-blind | 76 (placebo group) | >38°C | - | > 75 mg/L | 100% |

*Only with Incraft® endograft.

**Only with Zenith Alpha® thoracic endografts.

*** The sample only included percutaneous EVAR.

****Only with Anaconda® endograft.

^aThis group defined PIS as fever and leukocytosis and abdominal and/or back pain, or other nonspecific symptoms such as malaise or loss of appetite.

Table 1. Incidence of PIS according to definition.

following endovascular stent graft repair of aortic aneurysms. They defined PIS as a syndrome that occurs after EVAR and proposed two criteria for diagnosis: fever and leukocytosis. However, the cutoffs of these criteria are not specified. In their small study, they found seven patients (58%) to have leukocyte count superior to 11.000/μL, 10 patients (83%) to have fever greater than 38°C and 8 patients (67%) superior to 38.5°C. Indeed, in eight patients, CT revealed air within the native aorta, around the stent-graft and within the thrombus of the

excluded aneurysm. Physical examination, chest radiograph, urinalysis, urine culture and blood culture excluded any source of infection in 11 of 12 patients [2].

Gabriel et al. [13] analyzed the inflammatory response after endovascular repair of abdominal, thoracic and thoracoabdominal aortic aneurysms, but they neither define PIS nor stated its incidence. They found that peak values of sedimentation velocity, CRP and interleukin-6 were observed at 7 postoperative days, elevation of leukocytes count occurred in premature phase, while lymphocyte and platelet count occurred in a late phase of follow-up. Serum levels of creatinine did not have significant variability during follow-up (3 months) and fever occurred mainly in the period between 24 and 48 h after the surgery.

Chang et al. [14] studied the systemic inflammation, coagulopathy and acute renal insufficiency following endovascular thoracoabdominal aortic aneurysm repair (TAAA). They hypothesized that endovascular TAAA repair triggers a severe form of PIS. During the postoperative time, 18 of 38 patients (47%) developed fever ($>38.0^{\circ}\text{C}$) and all had statistically significant changes in leukocyte and platelet counts and prothrombin time. Once again, neither the definition nor the incidence was stated.

Georgiadis et al. [15] in their prospective study comparing the results of Endurant® endoprosthesis in hostile and friendly necks, pointed to a PIS incidence of 36.4% (28 patients, 9 patients in friendly neck group vs. 19 patients in hostile neck group; $p = 0.032$) with a mean duration of 2.02 days. However, the definition of PIS is unclear.

Two other studies described PIS incidence, but they did not clarify the definition used. Mazzaccaro et al. [16] performed a retrospective study with 10 patients who underwent EVAR, but only with Incraft® endograft. They found an incidence of PIS of 30% (three patients). However, they do not specify the definition that they used. Melissano et al. [17] evaluated retrospectively the safety and efficacy of the Zenith Alpha® (Cook Medical Inc., Bloomington, IN, USA), in thoracic endovascular aortic repair of thoracic aortic aneurysms, aortic ulcers and traumatic aortic rupture on 42 patients. They do not specify the PIS definition that they used but stated a PIS incidence of 2%.

Several studies defined PIS as a combination of two criteria: leukocytosis and fever. Arnaoutoglou et al. [1] performed a prospective study with 162 patients (148 with AAA and 14 with TAAA) who underwent endovascular aneurysm repair. PIS was defined according to definition of SIRS: presence of fever (continuous temperature $> 38^{\circ}\text{C}$) and leukocytosis ($>12,000/\mu\text{l}$) despite antibiotic therapy and negative culture results. PIS occurred in 49 patients (30.2%) and there were no significant differences in patients' characteristics and intra-operative variables, between the two groups. In this study, the authors did not characterize the population in detail and opted to describe consequences of PIS in six cases. In a subsequent prospective study of the same authors, with 40 patients, they found a similar incidence of PIS – 35% (14 patients). They did not also verify significant differences in patients' characteristics and intraoperative variables. Of note, a significant increase in IL-6 levels was observed only in the PIS group and the decrease in platelets count was greater in the PIS group, as was an increase in hs-CRP. The incidence of PIS varied according to the graft that was deployed, with highest incidences for Anaconda grafts (Vascutek-Terumo Cardiovascular System Corp, Ann Arbor,

MI, USA) with 100% of incidence, and Zenith grafts (Cook Medical Inc., Bloomington, IN, USA), with 50% of incidence. The Talent grafts (Medtronic Vascular AVE, Medtronic Europe SA, Route du Molliat, Switzerland) had an incidence of 37% (6/16 patients) and the Excluder grafts (W.L. Gore & Associates, Inc., Flagstaff, AZ, USA) had the lowest incidence with 12% (2/17 patients) [4].

Dosluoglu et al. [6] studied the feasibility and safety of ambulatory percutaneous EVAR in a sample of 79 patients. In this way, they compared the group in which the patients go home in the same-day of the procedure to the non-ambulatory-group and evaluate the incidence of PIS in these two groups. They defined PIS as any combination of fever $>37.8^{\circ}\text{C}$, white blood cell count $>10.000/\mu\text{l}$, abdominal and/or back pain, or other nonspecific symptoms such as malaise or loss of appetite. PIS occurred in 23% of the patients, 19% in the same-day discharge group and in 26% in non-ambulatory group.

In another study, with a retrospective design, of 118 patients who underwent EVAR but only with Anaconda endograft. These authors used the same definition of PIS with leukocytes $>12.000/\mu\text{l}$ and temperature and reported an incidence of PIS of 20.3% (24 patients) [8]. Another retrospective study with 87 patients, using the same definition for PIS, found an incidence of 39%. This value was not similar between graft types, with the highest incidence for Anaconda endograft (71%) and the least incidence in Excluder grafts (13%) [18]. Arnaoutoglou et al. [10] prospectively evaluated PIS after elective EVAR in 214 patients with AAAs and investigated its association with clinical outcome during first 30 postoperative days. The diagnosis of PIS occurred in 36% patients. They also used the same criteria described above for PIS.

With the same definition, Sartipy et al. [19] also investigated the impact of stent graft material on the inflammatory response, in 45 patients undergoing standard elective EVAR. The global incidence of PIS was 28%. A single-center, observational cohort study of 204 consecutive EVARs revealed an incidence of PIS of 31.4%, with the same definition [20]. In a similar way, Arnaoutoglou et al. [21] in a more recent prospective study with 182 consecutive EVARs, diagnosed PIS in 65 patients (35.7%).

Fewer studies defined PIS with elevation of CRP instead of leukocytosis. Voûte et al. [5] compared the effect of stent graft composition in PIS. This group defined the PIS as fever (tympanic temperature $>38^{\circ}\text{C}$) and elevated serum CRP level ($>10\text{ mg/l}$). They found an incidence of PIS of 56.1% (46 patients) for the woven polyester group and 17.9% (12 patients) for the ePTFE group ($p = 0.001$).

A randomized, double-blind, placebo-controlled trial was designed to analyze the effect of a single preoperative dose of 30 mg/kg of methylprednisolone or placebo, administered 2 h before surgery, in reducing the incidence of PIS after EVAR. They used the SIRS criteria for PIS (the presence of at least two of the following criteria: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; leukocytes $>12.000/\text{l}$, $<4.000/\text{l}$ or $>10\%$ bands; heart rate >90 ; respiratory rate >20 ; $\text{PaCO}_2 <32\text{ mm Hg}$), except the criterion of leukocytosis. Instead of leukocytosis, the criterion used was elevation of CRP $>75\text{ mg/L}$. PIS with modified SIRS criteria was present in 27% in the methylprednisolone group versus 100% in the placebo group [7].

Gorla et al. [22] developed a retrospective study and analyzed PIS incidence, but the 133 patients included underwent TEVAR due to type B acute aortic syndrome. The authors defined PIS as fever $>38^{\circ}\text{C}$, leukocytes $>12.000/\text{mL}$ and CRP $>10\text{ mg/dL}$ within 72 h after TEVAR, despite negative blood cultures. PIS was diagnosed in 15.8% of patients.

A German group studied the effects of antibiotics in preventing PIS after aortic endoprosthesis implant. This trial included 40 patients and they did not have an aneurysmal disease. In each group, there were 18 type B dissections and 2 penetrating aortic ulcers.

They compared the influence of perioperative single-shot versus prolonged (7 days) antibiotic therapy on parameters of PIS after thoracic endografting. There were no differences in parameters related to PIS, namely body temperature, leukocytes count and CRP, between two groups. They also did not find differences between the groups of acute and chronic type B dissections [23].

Moulakakis et al. [11] assessed the inflammatory and renal response after TEVAR in the descending thoracic aorta on 30 patients (28 aneurysms, 1 type B aortic dissection and 1 penetrating aortic ulcer). They do not evaluate the incidence of PIS but detected a significant increase in leukocytes, CRP, interleucin-6 and interleucin-10 at 24 and 48 h after endograft implantation compared to baseline; platelets were significantly decreased. This inflammatory response after TEVAR was associated to a rise in body temperature in the postprocedure period. Conversely, there were no significant differences in serum levels of interleucin-8, TNF- α , creatinine, urea or cystatin C after stent graft implantation.

In conclusion, many studies do not specify the PIS definitions, many others used the definition with leukocytosis and fever and only three studies used a definition that includes CRP. The reported incidences in literature vary greatly which is possibly a consequence of variability in definitions. Hence, the obvious need for a universal definition of this syndrome.

3. Etiology

The etiology of PIS is not entirely clear. Implant composition has been identified as one of the most important determinants of the incidence and severity of PIS. [4, 5] However, the inflammatory response is not of the same magnitude in all patients treated with the same type of endograft. So, factors other than implant material must also be responsible to the occurrence of PIS. These may be patient or implant related.

Lesion of the endothelium during implantation, bacterial translocation due to transient sigmoid ischemia, contrast medium-induced neutrophils degranulation, endovascular instrumentation of the mural thrombus and thrombosis of the aneurysm sac after aneurysm exclusion had all been proposed as factors that could trigger the pathophysiology of PIS [14, 23–26] (**Figure 1**).

3.1. Endograft material

This is the best investigated risk factor; several studies compared the incidence of PIS or the difference in inflammatory parameters and endograft material, mainly focusing on differences between polyester and expanded polytetrafluoroethylene (ePTFE)-based structures.

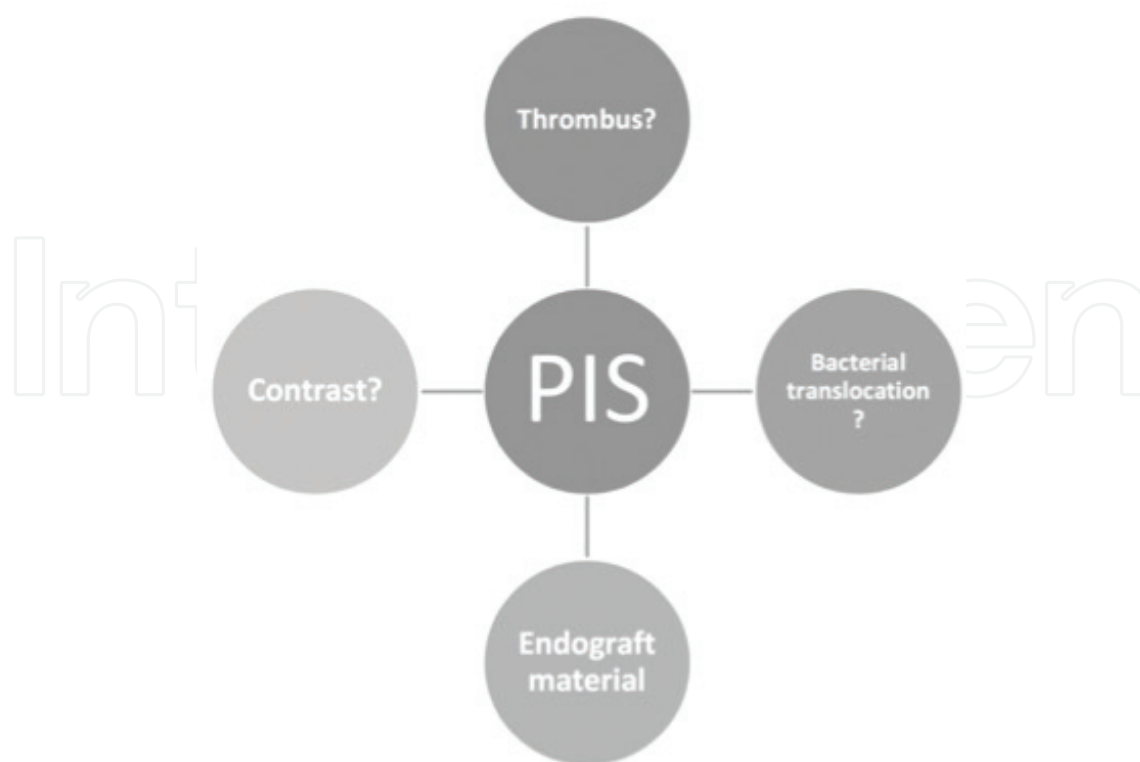


Figure 1. Multiple factors that may contribute to PIS occurrence.

The majority of the studies pointed to a higher incidence of PIS or a greater increase of inflammatory markers in polyester-based endografts [4, 5, 8, 18, 20]. Voûte et al. [5] constructed a multivariable risk model for PIS, and woven polyester constitution of the endograft was the only significant factor associated with an increased risk of developing PIS (HR 5.58; $p = 0.007$). Kakisis et al. [18] had similar results when testing for risk factors for PIS using a multivariable model; only the type of endograft was independently associated with the development of PIS.

Despite the results, another three studies could not identify a difference in the incidence of PIS between polyester and ePTFE endografts. [5, 11, 19] Gerasimidis et al. compared, prospectively, the incidence of inflammatory response between endovascular aneurysm repair with polyester devices (12 patients) and ePTFE devices (10 patients). One patient in each group had PIS, according to SIRS criteria. Three patients in the polyester group had fever ($>38^{\circ}\text{C}$) and only one patient in the PTFE group ($p < 0.005$). However, there were no statistically significant differences between two groups, for all endpoints, possibly due to sample size. Of note, all the patients in this study received a dose of an antihistamine (cetirizine hydrochloride 10 mg) before the surgery and nonsteroid antiinflammatory drugs (nimesulide 100 mg twice a day) during 72 h postoperatively [5]. In the study by Sartipy et al. [19] there were significant differences between the two types of graft material concerning fever and CRP, but there were no significant differences in the number of PIS events. It could also be related to sample size, with 32 patients treated with polyester grafts but only 13 patients with ePTFE grafts. They performed a sensitivity analysis that showed if three more patients in the polyester group would have developed PIS (or none instead of one patient in the PTFE group), the results would have reached significance. Lastly, Moulakakis et al. [11] assessed the inflammatory and renal response after TEVAR, and they did not observe a significant difference in

inflammatory response between polyester and PTFE groups. They attributed that to small number of patients implanted with ePTFE endografts in their trial.

In any case, PIS related to Anaconda® endografts had the highest incidence in published literature, except in one study by Nano et al. [8] in which the reported incidence was of only 20.3% [4, 18, 25]. In that study, however, isolated fever without any sign of infection and maintained for more than a week occurred in many patients, even after administration of corticosteroids (median duration, 11 days, (4–30 days)). In the same period in this hospital, PIS occurred with other endografts but lasted for less than 3 days or resolved completely after administration of corticosteroids [8]. Thus, it seems that in addition to the higher incidence of PIS, Anaconda® endografts are associated to a more intense syndrome, which is also more difficult to resolve.

Apart from fabric, other components of the graft structure could be implicated. The stent structure, for example, could influence the occurrence of PIS. As discussed by Voûte et al. [5] when comparing Endurant® and Talent® endografts, the Excluder graft, which is associated to the lowest incidence of PIS, has an additional outer layer of ePTFE, covering the alloy, whereas in others, the metal and fabric are connected by stitches. Moreover, the latter have a bare top stent which constitutes an additional amount of nitinol directly exposed to the circulation and to the vessel wall. In addition to amount of alloy exposition, the exact balance between nickel and titanium (components of nitinol) or even the way of cutting and polishing may differ between manufacturers and may influence the inflammatory reaction [5]. However, it is important to note that nitinol has been widely used in coronary and peripheral arterial “bare-metal” stents and no inflammatory response have been reported in these applications [27]. In Zenith® endograft, an additional component of stainless steel can contribute for the inflammatory response, but this has not been adequately studied.

Delivery systems could also theoretically influence PIS. Moulakakis et al. [25] showed that the Excluder® endograft had a milder postimplantation inflammation, compared to the others. In addition to differences of material composition, the Excluder® endograft is introduced through a sheath, in contrast to other endografts. They hypothesize that this may cause less injury to endothelium. Moreover, thickness and porosity may differ between polyester endografts, as the metallic skeleton, and can justify variability in inflammatory response after EVAR [25]. Despite all the proposed mechanisms, the only component of endografts that seems to influence the incidence of PIS significantly is the fabric. Polyester, when compared to ePTFE, results in a higher inflammatory reaction both in vitro and in vivo, and this is well replicated in aortic endograft implants [28].

3.2. Thrombus

The hypothesis that the amount of preexisting mural thrombus within the aneurysm sac could be related to PIS development derived from the finding that mural thrombus of an aortic aneurysm contains high levels of interleucin-6 [29]. In this way, it was conjectured that manipulations with endovascular material, as wires and catheters, in mural thrombus could release interleucin-6 and induce an inflammatory response. Nano et al. [8] reported an association between preoperative thrombus thickness and PIS with EVAR using the Anaconda®

endograft ($p = 0.001$). However, Kakisis et al. [18] rebutted this hypothesis, since they found that the volume of chronic mural thrombus did not affect any parameter of PIS. In the same line, in the study by Moulakakis et al. [25] the Anaconda® endograft had the highest inflammatory response and, simultaneously, requires less thrombus manipulation with catheters and wires during implant, once it has a magnet on the contralateral limb to facilitate its cannulation. If the mural thrombus was the main source to PIS, patients treated with the Anaconda® endograft should have the lowest incidence, and the contrary is observed.

Another hypothesis was that new-onset thrombus, instead of chronic mural thrombus, could be responsible for the acute inflammatory response [30]. Three authors tried to demonstrate this effect of new-onset thrombus but the results were not consistent. Kakisis et al. [18] could not find an association between the previous thrombus and PIS, but they found a significant correlation between the volume of new-onset thrombus and PIS parameters. In a multiple variable model, these authors showed that both the volume of new-onset thrombus and the type of endograft were independently associated with the development of PIS. However, Vöute et al. [5] analyzed the association between inflammatory response and new-onset thrombus after EVAR and found no significant correlation between new-onset thrombus and the rise in temperature ($p = 0.08$) or CRP ($p = 0.17$), with a larger patient sample. In the same way, Arnaoutoglou et al. [10] did not find differences regarding preoperative endoluminal thrombus or in the amount of newly formed thrombus between PIS and non-PIS patients groups. In light of the current evidence, it is not likely that chronic mural thrombus or new-onset thrombus within the aneurysm sac play a significant role in the development of PIS. It is possible that new onset thrombus may play a small role, which could not yet be clearly demonstrated due to sample size in all published studies on the subject.

3.3. Bacterial translocation

Another potential etiology for PIS after endovascular aneurysm repair is bacterial translocation due to transient sigmoid ischemia. Intestinal ischemia may be produced by either occlusion of a previously patent inferior mesenteric artery (IMA) or microembolization during catheter and wire manipulations. Thus, Kakisis et al. [18] analyzed the association between patency of the IMA and the postoperative temperature and inflammatory markers and found no significant correlation. Another trial, that studied the effects of antibiotic therapy in PIS after thoracic aortic stent placement, is in agreement [23]. The authors stated that there were no differences in parameters related to PIS, regardless of the duration of postoperative antibiotic therapy. Therefore, the hypothesis of bacterial translocation as a cause for PIS seems remote and there is no evidence to date to support it.

3.4. Contrast

Videm et al. [26] suggested that contrast medium iohexol provokes neutrophil degranulation, which is greatly enhanced when combined with stent graft material, contributing to PIS occurrence. There are other recent studies that specifically analyzed inflammatory response after endovascular aortic repair; however, they did not find any correlation between contrast use or dosage and PIS parameters [5, 8, 18, 25]. As such, this theory remains to be demonstrated.

3.5. Other factors

The influence of several other factors in PIS parameters has also been explored, namely age, gender, aneurysm size, extent of aortic coverage, length of operation, blood loss or transfusion, intensive care unit, statin, chronic obstructive disease, ischemic heart disease and heart failure. None has been shown to be an important factor to PIS [5, 8, 9, 14, 18].

4. Manifestations and diagnosis

PIS is characterized by fever, anorexia, fatigue and lumbar pain associated to increase in leukocytes count, CRP, decrease in platelets count and/or coagulation abnormalities.

It typically resolves within 2 weeks without any permanent ill effects, but in some cases may result in severe complications such as pulmonary dysfunction, cardiovascular events, renal insufficiency and multisystem organ failure [1, 14, 25].

The diagnosis might be suspected in the presence of fever without clinical source of infection in the immediate postoperative period after EVAR. However, the diagnosis of PIS will depend on definition that is adopted.

Fever is usually accompanied by a rise in laboratorial inflammatory markers and a drop in platelet count. Leukocytes count typically rises in the first postoperative day [5, 25]. CRP levels increase significantly between the first and third postoperative day [23, 31] (**Figure 2**).

In the presence of fever and inflammatory parameters in the early postoperative period, patients usually undergo a work-up for possible infection, typically including chest radiography, urinalysis, urine culture and blood culture [32]. Some argue that this may be costly and unnecessary in clinical absence of an infection source [33]. However, since consequences of a serious postoperative infection may be devastating, at least close observation is recommended.

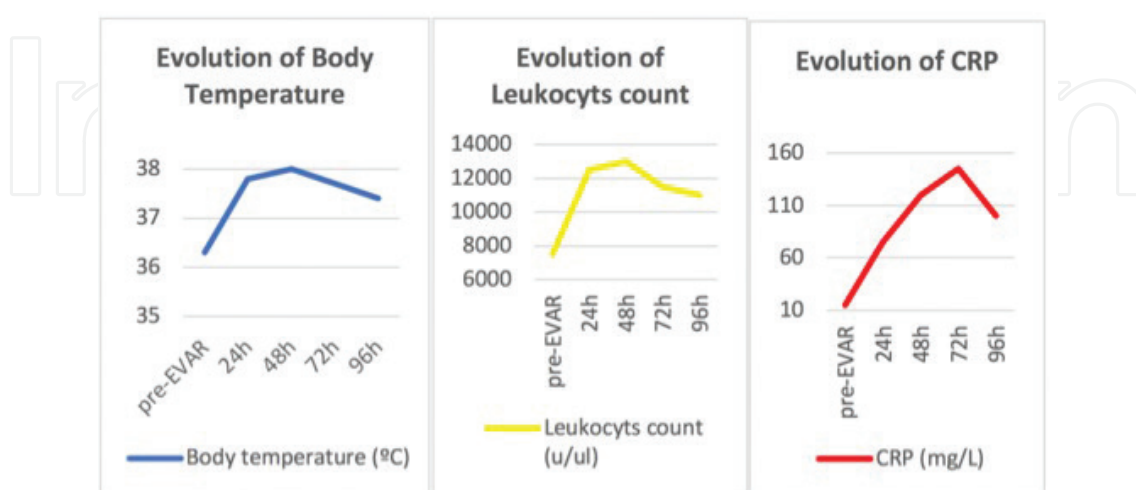


Figure 2. Evolution of body temperature, leucocytes count and CRP since EVAR until 96 h after the procedure. Adapted by Voûte et al. [5], Gabriel et al. [13] and Akin et al. [23].

Sartipy et al. [9] designed a prospective study to test the hypothesis was that procalcitonin would remain <0.5 ng/mL among patients who develop PIS after elective EVAR surgery, conversely to infectious complications. They defined PIS as a body temperature $> 38^{\circ}\text{C}$ and leukocytes $>12,000/\text{mL}$ at any time during the observation period combined with no other detected complication or any open surgical event explaining the inflammatory response. The global incidence of PIS in this trial was 17.5% (12 patients) but this incidence was higher in patients with polyester grafts than in PTFE grafts (22.4% vs. 5%). They verified that all PIS patients had levels of procalcitonin <0.5 ng/mL, as they hypothesized, whereas all showed an elevation on CRP >100 mg/L and leukocytes $>12,000/\text{mL}$.

Thus, procalcitonin appears as a good differentiator between PIS and infectious complications, probably less expensive and faster than microbiologic culture tests.

5. Clinical consequences

Several clinical consequences of PIS have been proposed, both in the early postoperative period and over follow-up (Table 2).

5.1. Prolongation of hospital stay/readmissions

Moulakakis et al. [11] did not find any clinical adverse events related to PIS and there were no readmissions in their study. In another study that evaluated inflammatory response to Anaconda® endografts, the patients who developed this syndrome had a longer hospital-stay [8]. Other studies showed a significant prolongation of postoperative hospitalization in the PIS group compared to non-PIS group [4, 10, 20].

Arnaoutoglou et al. [1] described six cases that required readmission, four cases due to a mild SIRS that resolves with non-steroidal anti-inflammatory drug orally, but the other two cases were a severe SIRS that required a stay in an intensive care unit and endovenous corticosteroids treatment.

In a study concerning the applicability of percutaneous ambulatory EVAR, one patient was also readmitted due to severe PIS in third postoperative day (in the non-ambulatory group) and PIS was the only reason for delayed discharge in five patients [6].

5.2. Renal dysfunction

Chang et al. [14] analyzed the systemic inflammation, coagulopathy and acute renal insufficiency following endovascular TAAA repair. These authors found that patients with postoperative renal insufficiency had higher changes in leukocytes and platelets counts, as compared with those who did not develop renal failure. Indeed, the two patients who died in first postoperative month developed acute renal insufficiency in the early postoperative period. The preoperative glomerular filtration rate < 60 mL/min/1.73 m² was not associated with the development of acute renal insufficiency ($p = 0.80$). They performed a univariate logistic regression analysis, which showed that each 5000 cells/ μL increase in leukocytes in

| Influence of PIS on Clinical Outcomes | | |
|--|--|---|
| | Studies suggesting adverse influence (authors, design, no patients) | Studies suggesting no influence (authors, design, no patients) |
| Hospital stay/ readmissions | 1. Arnaoutoglou <i>et al.</i> (1), Prospective, n=162 2. Arnaoutoglou <i>et al.</i> (4), Prospective, n=40 3. Nano <i>et al.</i> (8), Retrospective, n=118 4. Arnaoutoglou <i>et al.</i> (10), Prospective, n=214 5. Kwon <i>et al.</i> (20), Retrospective, n=204 | 1. Moulakakis <i>et al.</i> (11), Prospective, n=30 |
| Renal dysfunction | 1. Chang <i>et al.</i> (14), Prospective, n=38 | 1. Moulakakis <i>et al.</i> (11), Prospective, n=30 |
| Cardiovascular events | 1. Arnaoutoglou <i>et al.</i> (10), Prospective, n=214 2. Arnaoutoglou <i>et al.</i> (21), Prospective, n=182 | 1. Kwon <i>et al.</i> (20), Retrospective, n=204 |
| Endoleaks | 1. Kwon <i>et al.</i> (20), Retrospective, n=204 2. Gorla <i>et al.</i> (22), Retrospective, n=133 | 1. Voûte <i>et al.</i> (5), Retrospective, n=149 2. Nano <i>et al.</i> (8), Retrospective, n=118 3. Arnaoutoglou <i>et al.</i> (21), Prospective, n=182 |
| Quality of Life | 1. Nano <i>et al.</i> (8), Retrospective, n=118 | - |

Table 2. Summary table of the studies that favor influence of PIS in outcomes and of those that are against.

the postoperative period was associated with a 2.4-fold odds of postoperative renal insufficiency ($p = 0.02$). For platelets, each decrease of 50,000 platelets/ μL was associated with a 4.0-fold odds of postoperative renal insufficiency ($p = 0.02$). In opposition, Moulakakis *et al.* [11] stated that renal function was not influenced by the inflammatory response; no correlation was recognized between the increased inflammatory markers and renal function.

5.3. Cardiovascular events

In a study that analyzed the influence of inflammatory reaction after endovascular aneurysm repair in 30-day outcomes, a multiple logistic regression model revealed that coronary artery disease ($p = 0.01$), post-operative hs-CRP ($p = 0.001$) and duration of fever ($p = 0.02$) independently predict major cardiovascular events. For every additional day of fever after the first, the chance of a cardiovascular episode increased by 67.9% ($p = 0.017$) and for every 10 units increase of hs-CRP, this probability increases by 15% ($p = 0.001$). For all adverse events studied, namely cardiovascular events, acute renal failure, readmission and death by any cause, multiple logistic regression analysis showed that postoperative hs-CRP ($p = 0.004$), PIS ($p = 0.01$), maximum temperature ($p = 0.02$) and smoking history ($p = 0.02$) were independent predictors. Postoperative hs-CRP revealed an important predictor for adverse outcomes during the first 30 days. A threshold value of 125 mg/L was highly associated with an adverse event, with a sensitivity of 72% and specificity of 75% [10].

In a prospective study of 182 consecutive EVARs, patients were monitored during a year. Several adverse events are scrutinized, such as any major adverse cardiovascular events, acute renal failure, readmission and death from any cause. During the follow-up period, major adverse cardiovascular events occurred in 17.2% patients in PIS group vs. 4.3% in non PIS group and the other adverse events occurred in 18.8% of patients vs. 5.1%, respectively.

Multiple logistic regression analysis showed that the occurrence of PIS was the only independent predictor of major adverse cardiovascular events ($p = 0.007$) or any adverse event ($p = 0.005$). Patients with the diagnosis of PIS were about 4–5 times more likely to suffer of a major cardiovascular event or another adverse event, than non-PIS patients [21].

Conversely, Kwon et al. [20] stated that patients with and without PIS had similar long-term overall survival rates and other clinical outcomes, such as systemic or implant-related complications.

5.4. Endoleaks

In the study by Voûte et al. [5] the change in PIS parameters did not correlate to postoperative endoleaks. Besides prolongation of hospital stay, Nano et al. [8] also established a benign character for the PIS; no association between PIS and onset of early and long-term complications, namely endoleaks, was reported.

Gorla et al. [22] studied a composite endpoint of major adverse events, such as aortic rupture, need for reintervention and all-cause mortality, after TEVAR of type B acute aortic syndromes. The mean follow-up was 4.0 ± 2.9 years. The major adverse events were more frequent in the PIS than in the non-PIS group (62.5 vs. 25.9%; $p = 0.004$).

Kwon et al. [20] in a study with a follow-up of 44 months, PIS was significantly associated with a decreased risk of developing type II endoleaks ($p = 0.044$). PIS appeared to be beneficial in preventing type II endoleaks during postoperative period. Kaplan–Meier survival analysis showed that the groups (PIS and non-PIS) had similar rates of overall survival ($p = 0.761$) and other clinical outcomes ($p = 0.562$), except the rate of secondary procedures that was significantly higher in the non-PIS group ($p = 0.049$).

Arnaoutoglou et al. [21] in a prospective study with 1 year-follow up, found no correlation between endoleak or any complication rates and PIS ($p > 0.05$).

5.5. Quality of life

The analysis of the questionnaires on quality of life after 1 month of the surgery showed that PIS patients felt significantly more limited in their daily physical activities after surgery, as well as more emotionally discouraged and depressed/anxious about their state of health [8]. No long-term studies involving quality of life are available to date.

In summary, there is a suspicion that PIS may be involved in a higher rate of early cardiovascular complications and worse early quality of life. There is no evidence to date that suggests a worse long-term outcome for patients affected, but the data are scarce.

6. Prevention and treatment

The 30 day-outcomes of patients with PIS described by Arnaoutoglou et al. [10] suggest that a specific treatment should be adopted to PIS to avoid clinical consequences. Akin et al. [23] tested the extension of antibiotherapy during the postoperative time, but it did not show

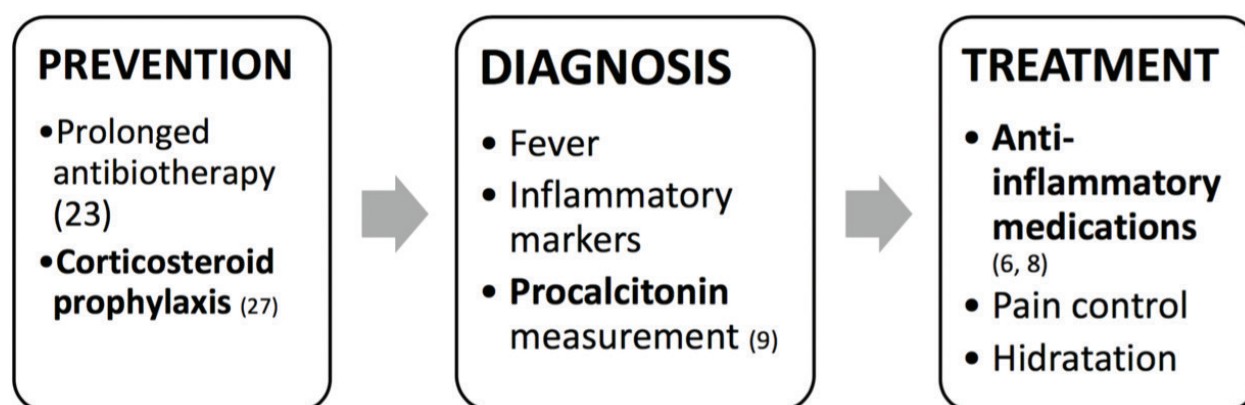


Figure 3. Schematic diagram of prevention, diagnosis and treatment of PIS, with associated references.

any advantage in PIS incidence. In the study by Nano et al. [8] in case of PIS diagnosis, 1 g of hydrocortisone was administered intravenously on the third postoperative day, according to institutional protocol. In another study with patients who underwent percutaneous ambulatory EVAR, one patient had to be readmitted due to a severe PIS in third postoperative day. He was managed with hydration, pain control and anti-inflammatory medications and went home again after 3 days [6].

DelaMotte et al. [7] in a randomized, double-blind, placebo-controlled trial involving 153 patients, analyzed the effects of a single preoperative dose of 30 mg/kg of methylprednisolone or placebo, administered 2 h before surgery. For diagnosis of PIS, they used all criteria of SIRS, except for leukocytosis that was changed to CRP elevation due to the influence of corticoid therapy on leucocyte count and they obtained, with a single preoperative dose of methylprednisolone, a reduction in PIS from 100–27% [7]. The postoperative need for morphine was significantly reduced by methylprednisolone but the need for antiemetics was similar. There were no differences in 30-day medical morbidity (13 vs. 43%), surgical morbidity (20 vs. 43%), reinterventions (0 vs. 29%) or readmissions (7 vs. 14%) in the methylprednisolone versus placebo group. There was no 30-day mortality in all the patients included, and during the 3 months of follow up, there was no significant difference in mortality between the groups (3% vs. 1%, $P = 1.0$). Regarding adverse effects of corticosteroids, 11 potential methylprednisolone side effects occurred in 10 patients (14%). They were mainly related to infusion of the drug: metallic taste in five patients, flushing in three patients, rise in blood pressure requiring treatment in two patients and euphoria within the first 24 h in one patient. In the placebo group, rise in blood pressure was noted in one patient. Analyzing the subgroup of diabetic patients (15 patients in methylprednisolone group and 7 patients in placebo group), the intraoperative median blood glucose levels were higher in the methylprednisolone group than in the placebo (363 mg/dL vs. 298 mg/dL ($p = 0.01$)) and they remained higher during the first 24 h ($p = 0.006$). In 47% of patients in the methylprednisolone group, supplementary insulin was necessary compared to none in placebo group during the first 24 h. There were no records of adverse events relating to dysregulation of blood glucose levels. Subgroup analysis on the diabetic patients showed the same tendencies as in the entire cohort [7]. In this trial, there was a substantial difference between PIS incidence with a single preoperative dose of methylprednisolone. However, they

defined PIS as having either fever or elevated CRP levels. Hence, possibly, the higher incidence of 100% in placebo group.

The routine administration of drugs like steroids or nonsteroid anti-inflammatory drugs is of concern because of their side effects, mainly in patients with multiple or more severe comorbidities [1]. However, it seems reasonable to prevent this inflammatory response, once it can lead to prolonged hospitalization or a readmission and even to more severe consequences, as the authors described above.

Undoubtedly, future studies have to be performed to clarify the need for routine prophylaxis for this syndrome or a symptom based anti-inflammatory therapy (**Figure 3**).

7. Conclusion

The absence of a universal definition for PIS is responsible to the variability of its incidence. However, CRP seems to be a better criterion for PIS instead of leukocyte count. The etiology is still not clarified, but the majority of the studies pointed to a relevant role for endograft material. Regarding diagnosis, procalcitonin appears to be a good differentiator between PIS and infectious complications. The clinical consequences of this syndrome, in length of hospital stay, readmissions, renal function, cardiovascular events, endoleaks and quality of life, are not fully elucidated, and more studies have to be performed. However, there is evidence suggesting a prolonged hospital stay, higher risk of early cardiovascular events and worse early quality of life for affected patients. Regarding treatment, although corticosteroids and nonsteroidal anti-inflammatory drugs seem to be a reasonably effective strategy, there is a need to establish the best treatment and whether pharmaceutical prophylaxis is necessary. The routine administration of drugs like steroids or nonsteroid anti-inflammatory drugs raises concerns due to side effects, mainly in patients with more severe comorbidities.

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