Aortic infections

The Nadir of Vascular Surgery

KARL SÖRELIUS
Abstract


Aortic infections are rare, life-threatening and constitute a major challenge in surgical management. This thesis aims to evaluate short – and long-term outcome of endovascular aortic repair (EVAR) for mycotic aortic aneurysms (MAA) and the subsequent risk of recurrent infections, changes in surgical practice over time for abdominal MAAs in Sweden and outcome for different treatment modalities, as well as the risk of secondary vascular infection after treatment with Open abdomen after aortic surgery.

Paper I, a retrospective single centre study of patients with MAA treated with EVAR, demonstrated a good short-term outcome, 91% survival at 30-days, and acceptable mid-term survival, 73% at 1-year.

Paper II, a retrospective international multicentre study of patients treated with EVAR for MAA, confirmed the results in paper I, and showed that EVAR is feasible and for most MAA patients a durable treatment option, 5-year survival was 55% and 10-year 41%. A total of 19% died from an infection-related complication, mostly during the first postoperative year. Non-Salmonella-positive culture was a predictor for late infection–related death.

Paper III, a population-based cohort study on all abdominal MAAs operated on between 1994-2014 in Sweden. Overall survival was 86% at 3-months, 79% at 1-year and 59% at 5-years. The survival was significantly better after endovascular compared to open repair up to 1-year without increasing recurrence of infection or reoperation, thereafter there was no difference. After 2001 EVAR constituted 60 % of all repairs, thus indicating a paradigm shift in treatment for abdominal MAAs in Sweden.

Paper IV, a prospective multicentre study of patients treated with open abdomen after aortic surgery. Infectious complications, such as graft infections, occurred after intestinal ischaemia and prolonged OA-treatment, and were often fatal.

Keywords: Mycotic, aortic, aneurysm, surgery, infection, endovascular repair, open abdomen

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I had to get off the boat, so I could walk on water

– Sean Carter, 2004
To my parents
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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Contents

Introduction .................................................................................................................. 11
Mycotic aortic aneurysms ............................................................................................. 12
  A brief history ........................................................................................................... 12
  Nomenclature ......................................................................................................... 13
Pathophysiology ........................................................................................................ 15
  Histology .................................................................................................................. 18
  Bacteriology ............................................................................................................. 18
  Salmonella and the aorta – an unrequited love story ............................................ 20
  Other microorganisms ............................................................................................ 21
Epidemiology .............................................................................................................. 22
  Incidence and Patient characteristics .................................................................... 22
  Prognosis ................................................................................................................ 22
Diagnosis ..................................................................................................................... 24
  Clinical presentation ............................................................................................... 24
  Laboratory findings ............................................................................................... 25
  Radiological findings ............................................................................................. 25
Management .............................................................................................................. 27
  Open surgical treatment ........................................................................................ 27
  Endovascular treatment ......................................................................................... 30
  Antibiotics ............................................................................................................... 32
  Adjunctive procedures ........................................................................................... 32
  Risk factors for adverse outcome and persistent infection .................................. 33
Other infected arterial aneurysms ............................................................................. 34
Open abdomen .......................................................................................................... 35
  Definitions .............................................................................................................. 35
  Pathophysiologic effects of IAP elevation ............................................................ 35
  Incidence of IAH/ACS after aortic surgery ......................................................... 36
  Management of IAH/ACS ...................................................................................... 36
  OA as a concept ..................................................................................................... 37
  OA and the risk of vascular infection .................................................................. 37
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>Aortic aneurysm</td>
</tr>
<tr>
<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
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<tr>
<td>ABx</td>
<td>Antibiotic therapy</td>
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<td>ACS</td>
<td>Abdominal compartment syndrome</td>
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<tr>
<td>AEF</td>
<td>Aorto-enteric fistula</td>
</tr>
<tr>
<td>APP</td>
<td>Abdominal perfusion pressure</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>EAF</td>
<td>Entero-atmospheric fistula</td>
</tr>
<tr>
<td>EVAR</td>
<td>Endovascular aortic repair</td>
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<tr>
<td>FDG</td>
<td>Fluorodeoxyglucose</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>iAAA</td>
<td>Intact abdominal aortic aneurysm</td>
</tr>
<tr>
<td>IAH</td>
<td>Intra-abdominal hypertension</td>
</tr>
<tr>
<td>IAP</td>
<td>Intra-abdominal pressure</td>
</tr>
<tr>
<td>MAA</td>
<td>Mycotic aortic aneurysm</td>
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<tr>
<td>MAAA</td>
<td>Mycotic abdominal aortic aneurysm</td>
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<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>OA</td>
<td>Open abdomen</td>
</tr>
<tr>
<td>OR</td>
<td>Open repair</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>rAAA</td>
<td>Ruptured abdominal aortic aneurysm</td>
</tr>
<tr>
<td>TAAA</td>
<td>Thoraco-abdominal aortic aneurysm</td>
</tr>
<tr>
<td>TAC</td>
<td>Temporary abdominal closure</td>
</tr>
<tr>
<td>VAWC</td>
<td>Vacuum assisted wound closure</td>
</tr>
<tr>
<td>VAWCM</td>
<td>VAWC and mesh-mediated fascial traction</td>
</tr>
</tbody>
</table>
Introduction

In the brief history of vascular surgery, the nemesis has been infection due to its dire consequences. This will be the theme for this thesis, and in particular mycotic (infected) aortic aneurysms. Throughout this thesis, both the terms mycotic and infected aneurysm will be used interchangeably, referring the same entity. The dual nature of mycotic aneurysms – the vascular and the infectious – makes for delicate problems in diagnosis as well as treatment. The overall aim of the thesis is to investigate surgical management for mycotic aortic aneurysms, in particular endovascular aortic repair, and also the risk of vascular infection after aortic aneurysm repair with subsequent OA-treatment.

Nadir, as in the title, is the direction opposite of zenith, and is used as a metaphor for expressing that the features of infections of the largest artery of the human body are not bright, but precarious.
Mycotic aortic aneurysms

A brief history
The term “mycotic aneurysm” is a misnomer for infection, usually bacterial, which degrades the aortic wall with subsequent aneurysm development. The term is imprecise, whilst implicating a fungal genesis, which is extremely rare. The term is being used because it is generally recognized and has the advantage of common usage. A more appropriate term would be infected aneurysm. The term mycotic originates from 1885, when sir William Osler, in his famous Gulstonian lectures, described a patient with fever and pneumonia in whom an autopsy revealed aortic valve vegetations and four aortic aneurysms with fungal shaped appearances, and has since been the name given to this group of aneurysms which arise in various ways from infection in the aortic wall (Osler 1885).

The French surgeon Ambroise Paré had as early as in the 16th century noticed an association between arterial aneurysms and syphilis. Virchow first observed in 1847 that arterial integrity can be disrupted by the presence of septic embolus (Virchow 1847). In 1851 Koch reported an infected aneurysm engaging the superior mesenteric artery (Koch 1851). Shortly after Osler, Ponfick in 1873 and Eppinger in 1887, performed the first anatomical examinations of aneurysms caused by embolism, and Eppinger first used the term embolo-mycotic to describe the relationship of both an infectious agent and an embolus to the development of aneurysms (Ponfick 1873, Eppinger 1887). In 1909 Lewis and Schrager described a mycotic aneurysm associated with arterial degenerative disease (Lewis 1909) and in 1923, Stengel and Wolferth showed that infected aneurysms may occur in a variety of septic conditions other than endocarditis (Stengel 1923). Later in 1956, Hawkins and Yeager suggested that the concept of lodgement of bacteria might occur at sites of intimal disruption caused by atherosclerosis (Hawkins 1956). Round the same time, in 1954, Barker recognized the dire consequences of mycotic aneurysms that were treated non-operatively and recommended prompt surgery (Barker 1954). Somewhat ironically, the first patient successfully treated for a mycotic aortic aneurysm was with open surgical excision and in situ graft for revascularisation in 1962 by Sower and Whelan (Sower, 1962), and with endovascular approach in 1998 by Semba (Semb 1998). In 1989 the first HIV-related aneurysm was described (Sinzobahamvya 1989). Various definitions such as “primary mycotic aneurysm”, “cryptogenic mycotic aneu-
rysm” and “SAP (septic aortic pseudoaneurysm)” have been proposed, with different criteria for inclusion and exclusion (Crane 1937, Blum 1962, Patel 1977, Reddy 1989 for Rutherford 3rd ed.), whereas the classification of “spontaneous arterial aneurysms” by Wilson in 1978 is still prevailing (Wilson 1978), see Pathophysiology, but the absence of uniform terminology is striking.

A huge difficulty for all aforementioned pioneers, as well as for our research group, while studying this disease is its rarity, making population-based, randomized controlled trials and robust statistical analysis difficult.

Nomenclature

An arterial aneurysm is a local widening of at least 50% of the artery. In an aortic aneurysm, the diameter has to exceed a certain diameter (Wanhainen 2008). The shape of aneurysms may be fusiform, saccular or multi-lobular. Most arterial aneurysms are the result of a degenerative inflammatory process, in which degradation of the vessels’ connective tissue is a key element. These aneurysms are commonly fusiform in shape. The exact pathophysiological mechanism is not known but is thought to involve multiple pathways on cellular level. Although several risk factors have been identified, the main being high age, smoking, male sex, heredity and atherosclerosis. The weakening of the arterial wall leads to an expansion of the artery with an increased diameter. In degenerative aneurysms the expansion rate is slow, and may take years up to decades. This process is silent, that is, it goes without symptoms. But at a certain diameter the tension of the aneurysm wall exceeds its strength, and at this point the aneurysm ruptures. The individual bleeds internally and gets symptomatic; severe abdominal/back pain, circulatory failure and eventually death (Rutherford 8th edition).

In a mycotic (infected) aneurysm, the degenerative process of the arterial wall is a result of a rapid, on-going infection in the arterial wall. The process is not silent, but goes with a variety of symptoms and the most frequent being pain and fever (Mundth 1969). Most mycotic aneurysms are saccular or somehow eccentric in shape (Weintraub 1968). There are no established guidelines on how to measure a saccular aneurysm, and hence there is no diameter limit. Whether the term mycotic should be replaced by infected has been debated the last 50 years. Here, to avoid confusion both terms are being used synonymously. It is common in the literature to mix other infectious conditions involving the aorta, such as graft infection and aorto-enteric fistulae, with mycotic aneurysms. This thesis will end in a strong plea for a more modern and precise terminology to facilitate research and understanding around this disease.
Figure 1. Fusiform, saccular and multi-lobular aneurysms. An MAA may present in any of these shapes, but predominantly as saccular or multi-lobular aneurysm.

Figure 2. Thoracic mycotic aortic aneurysm with saccular shape.
Pathophysiology

The normal, healthy aortic wall is extremely resistant to microbial infections. However, the diseased aortic vessel wall may be predisposed to lodgement and growth of pathogens, especially bacteria. Predisposing aortic conditions may be atherosclerosis, syphilis or cystic medionecrosis (Parkhurst 1955, Zak 1958, Sommerville 1959, Williams 1952).

Aortic aneurysms due to infection are predominantly caused by bacteria, but there are a few reports of fungal infected aneurysms (Parameswaran 2008) and there seems to exist a special type in HIV-positive patients (Nair 2000). There are different subgroups of mycotic aortic aneurysms, see Table 1. The exact mechanism of interaction between the bacteria and the vascular endothelium in the aorta has yet not been established. It is thought to be effected in conformity with the development of infected native heart valves. Bacteria, which have entered into the blood stream via the oropharynx, gastrointestinal tract or genitourinary system adhere poorly to the healthy endothelium. But when the endothelium is damaged, eg by atherosclerosis, platelets, fibrin and red blood cells are accumulated. Fibronectin, an extracellular glycoprotein receptor, is expressed by the endothelium, fibroblasts and platelets in response to the vascular injury. Fibronectin may then simultaneously bind fibrin, collagen, human cells and bacteria. Many bacterial species have fibronectin receptors including *Stahylococcus* sp and *Streptococcus* sp. This may be one of multiple pathways the bacteria adhere to the endothelium and then infect the vessel wall (Chavakis 2005). The role of biofilm in native aorta is unclear (Kokare 2008).

In the pre-antibiotic era a vast quantity of infected aortic aneurysms were due to tertiary syphilis, caused by a bacteria *Treponema pallidum*. In the tertiary stage of syphilis the disease progresses onto the aorta, syphilitic aortitis. Syphilitic aortitis typically involves the thoracic aorta. Initially the inflammation involves the adventitia, affecting the vasa vasorum, which become hyperplastically thickened causing obliterative endarteritis and necrosis. At the focal point of infection the aorta eventually becomes ischemic and the aortic wall weakens, and with disease progression an aneurysm forms. Syphilitic aneurysms are today, after the introduction of antibiotics, a rarity (Jackman 1989, Lande 1976) and its pathophysiologic mechanism very different from today’s infected aneurysms.

In 1978 Wilson et al divided infected aneurysms into four subgroups based on their etiology; mycotic aneurysms from septic emboli, microbial
arteritis with aneurysm formation, infected pre-existing aneurysm and post-traumatic infected false aneurysm, see table 1 (Wilson 1978). Infected aneurysms may also develop secondary to contiguous infection such as graft infection, aortoenteric fistula or abscess. This last entity also belongs to the panorama of aortic infections but will not be discussed here, other than as complications to MAA.

Table 1. Classification of infected aneurysms based on etiology according to Wilson et al. (1978). *The last column, with heading HIV-related aneurysm, has been added by the author of this thesis.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Myotic aneurysm</th>
<th>Infected aneurysm</th>
<th>Microbial arteritis</th>
<th>Traumatic infected aneurysm</th>
<th>HIV-related aneurysm*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td></td>
<td>Bacteremia</td>
<td>Bacteremia</td>
<td>Trauma/punction</td>
<td>HIV</td>
</tr>
<tr>
<td>Sex</td>
<td>F&gt;M</td>
<td>M</td>
<td>M</td>
<td>M or F</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>30-50</td>
<td>Over 50</td>
<td>Over 50</td>
<td>Under 30</td>
<td>Round 30</td>
</tr>
<tr>
<td>Incidence</td>
<td>Rare</td>
<td>Unusual</td>
<td>Common</td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td>Location</td>
<td>Any vessel</td>
<td>Distal aorta</td>
<td>Aortoiliac</td>
<td>Femoral, carotid</td>
<td>Any vessel</td>
</tr>
<tr>
<td>Number</td>
<td>Multiple</td>
<td>Single</td>
<td>Single</td>
<td>Multiple</td>
<td>Multiple</td>
</tr>
<tr>
<td>Bacteriology</td>
<td>Gram+ cocci</td>
<td>Staph., E.coli</td>
<td>Salmonella sp.</td>
<td>Polymicrobial</td>
<td></td>
</tr>
</tbody>
</table>

According to Wilson’s classification, the subgroup of mycotic aneurysms develop when a septic emboli from a diseased heart of infective endocarditis lodges in the vasa vasorum of the artery and initiates a degrading process in the wall of the vessel. Septic emboli might affect every possible artery throughout the body. This subgroup was the most common in the pre-antibiotic era, but thanks to antibiotics and decline of rheumatic fever and advances in valve surgery it is today a rarity.

Microbial arteritis is today the most common form of mycotic aneurysms and mainly affects the elderly population (Brown 1984, Reddy 1991). The normal, healthy intima is highly resistant to blood-borne bacteria, but when aged and transformed by atherosclerosis it becomes immuno-compromised and bacteria may enter the vessel wall through intimal disruption caused by the atherosclerosis itself. Supporting atherosclerosis as the principal predisposing factor is the fact that the aorta, the most frequent site of atherosclerosis, is three times more prone to develop these infected aneurysms than peripheral arteries (Mundth 1969, Singh 1972). In addition, 70% of patients with microbial arteritis are in immuno-compromised state, either by disease or treatment (Johansen 1983, Sriussadaporn 1996).
Infected preexisting aneurysms are existing degenerative aneurysms that become infected by blood-borne bacteria (Sommerville 1959). This entity is not to be confused with degenerative aortic aneurysms that are colonized by bacteriae, showing on cultures from the aortic wall or in the microscopic examination, but without clinical signs of infection (Fourneau 1996).

Post-traumatic infected false aneurysms are mainly due to intended vein injections in drug addicts and iatrogenic arterial puncture in susceptible individuals. The most common sites of these infected, false aneurysms are the femoral artery, the subclavian- and the carotid artery (Geelhoed 1974).

Degenerative aortic aneurysms mainly develop in the infrarenal part of the aorta, while MAAs occur throughout the aorta. The suprarenal part is affected in approximately 60% of all cases (Miller 1994), which partly may be explained by a higher count of vasa vasorum and more atherosclerosis in the proximal part of the aorta.

In addition to Wilson’s grouping of infected aneurysms there has emerged one more group which should be included, HIV-related aneurysms. These aneurysms are seen in young patients with advanced staged HIV-infection, median age of 30 with multiple aneurysms throughout the arterial system but predominantly in peripheral arteries, mainly the carotid and superficial femoral artery. The precise pathogenesis is unclear, but histology shows adventitial changes resembling those seen in syphilitic aneurysms with adventitial involvement with occlusion of the vasa vasorum. There is no evidence of direct viral action leading to arterial wall destruction, although viral proteins have been demonstrated in biopsies. Authors first hypothesized that bacteraemia, due to advanced HIV-infection and secondary immunosuppression, lodged in the arterial wall, much like the process in microbial arteritis. Failure to demonstrate microorganisms in culture and microscopic examinations has made this explanation less likely. (Marks 1995, Chetty 2000, Nair 2000) A casual viral-aneurysm relationship can for the time being not be inferred or excluded. Most work on this originates from Nair and coworkers in Durban in the province of KwaZulu-Natal in the Republic of South Africa, suggesting a specific gene predisposing this manifestation of advanced HIV.

Since this thesis focuses on mycotic aortic aneurysms and not peripheral mycotic aneurysms, it is mainly the subgroup of microbial arteritis, but also to some extent infected pre-existing aneurysms and mycotic aneurysms from septic emboli that are the objects.

An MAA may be complicated by development of an aorto-enteric (AEF) or aorto-bronchial fistula. These two subgroups of patients have a particularly poor prognosis.
Histology

There are few histopathologic studies on infected aneurysms, and most are dated and derived from autopsy series or case reports.

Once infection is established in the aortic wall, the acute inflammatory response seems to occur rapidly. The most characteristic findings are loss of the intima, destruction of the elastic tissues, especially the internal elastic lamina and acute or subacute periarteritis or mesarteritis. In some cases the border between affected and unaffected tissue is abrupt. Infiltration of acute inflammatory cells, in particular neutrophils with abscess formation may be seen in the aortic wall which destruct the layers of the intima and the media. This process leads to fast transmural inflammation, erosion, aneurysmal dilatation and eventually rupture. The inflammatory response in the infected aneurysm is more severe at the site of rupture. Studies of MAAs not associated with infective endocarditis or infection in adjacent structures showed presence of additional aortic disease including atherosclerosis, syphilitic aortitis and cystic medionecrosis (Bennett 1967, Sommerville 1959, Parkhurst 1955, Miller 2004, Jarrett 1975, Stengel 1923). In HIV-related aneurysms, the principal features are those of adventitial involvement with acute and chronic inflammatory cell infiltrate centered in the vasa vasorum with subsequent occlusion. The inflammation largely spares the media and intima. Immunohistochemical staining confirms HIV protein within lymphocytes in the aneurysm wall (Chetty 2000).

This section does not include the histopathology of syphilitical aneurysms.

Bacteriology

The etiology of MAA has changed considerably since the time of Osler. Since antimicrobial therapy made its way in the 1940s, infected aneurysms secondary to syphilis and embolic seeding from infected cardiac valves have become unusual causes (Jarrett 1975). In 1923 Stengel and Wolferth reviewed 217 cases of mycotic aneurysms. The gender distribution was 68% males, and 85% were below 40 years of age. In 187 of these there were evidence of bacterial endocarditis and in 30 there were not. The artery most frequently involved was the aorta (n=66), and 22.5% had multiple aneurysms. They state that: “apparently the arterial walls don’t furnish a favorable habitat for them (the bacteria) as the heart valves do for they tend to disappear from the aneurysms”. Unfortunately this excellent article does not account in detail for the bacteriology, but state that the organisms most frequently recovered were non-hemolytic streptococci, staphylococci and that various rod forms have been seen but not been cultured.
In 1955, Parkhurst reviewed 22792 necropsies at Boston City Hospital between 1902 until 1951. In these cases 338 aortic aneurysms were found; 143 were syphilitic and nine mycotic (according to the definition then prevailing), the remaining non-infected. Parkhurst observed a sharp drop of syphilitic incidence from 52-70% between 1902 and 1941, to 25% between 1942 and 1951.

Today the causative bacteriologic spectrum may be divided in two groups based on geography; the European/North American and the East Asian (Taiwan, China and Singapore), see table 2 and 3. There are hardly any reports on MAAs from South America, Africa or Australia, an exception being HIV-related aneurysms where most reports come from the Republic of South Africa.

**Table 2, left and table 3, right.** Bacteriology in East Asia, left*, and Europe/North America, right**.

![Pie charts showing bacteriology in East Asia and Europe/North America.](chart)


In Europe/North America *Staphylococcus sp, Streptococcus sp, Salmonella sp*, and *E.coli sp* are the most common, while in East Asia *Salmonella sp.* is the dominant pathogen. Recently, it has been documented that gram-positive infections are more frequent than gram-negative infections causing sepsis (Remick 2007), which might explain the bacteriology of MAAs in Europe/North America.

Why *Salmonella sp.* are dominant in East Asia and one of the main pathogens also in Europe/North America will be discussed in a separate chapter, see next. Thus, gram-positive cocci and gram-negative rods are the most prevalent organisms causing MAAs.

The high rate of negative cultures, 17%, in both groups may be due to the fact that anaerobic cultures are difficult to obtain and that patients often have been on broadspectrum antibiotics prior to culture. In fact, in many series the
rates of negative cultures are even higher. The complexity of this fact and the
certainness about the diagnosis will be discussed further in the Diagnosis
chapter. It is highly interesting that Stengel and Wollerth made this observ-
ation as early as in the 1920s. Reddy et al reported in 1991 positive blood
cultures in 69% of MAAs and positive aneurysm wall culture in 92% of their
patients (Reddy 1991).

Adding further to this complexity is that routine cultures from non-
infected aortic aneurysms may yield a positive result in 14-37% of cases
(Farkas 1993, Forneau 1996, Eriksson 1982, Ernst 1977). In these papers
about 90% of the microorganisms were gram-positive, and the authors con-
cluded that positive cultures from aneurysm without rupture or signs of in-
fection were not a risk factor for secondary graft infection and have no path-
ogenic significance or therapeutic implication. Thus, a positive culture
(blood and/or aortic tissue) alone is not sufficient for the diagnosis MAA.

Salmonella and the aorta – an unrequited love story

Salmonella, first reported in 1886, by Salmon and Smith, are non-
encapsulated, intracellular, non-spore-forming gram-negative, facultative
anaerobic rods (Salmon 1886, Coburn 2006). Salmonella follows a cyclic
lifestyle in which host colonization is alternated with periods of survival
outside the host. It seems that biofilm formation contributes to both host
colonization as well as to its survival in non-host conditions (Steenackers
2011). Salmonellae are of the family Enterobacteriaceae. Except for one
serotype Salmonella sp. are motile using flagella. Three species of Salmonel-
la exist: S.typhi, S.choleraesuis and S. enteriditis. A single serotype of the
two former species exists, but there are more than 1700 serotypes of the last
one. Salmonella typhi and Salmonella paratyphi (S. enteriditis), cause ty-
phoid fever which is completely different from other salmonella infections,
and infect only humans and can therefore only be acquired via fecal-oral
route, from an infected person or a chronic carrier. There are several sub-
groups of Paratyphi.

Non-typhoidal salmonellae are widely disseminated in nature and com-
monly associated with some animals (chickens and turtles). Sources for hu-
man infections are usually food products. Human to human transmission of
Non-typhoidal salmonellae plays a negligible role, since most are acquired
through foods (Cohen 1978, Chiu 2004). The incidence of infections with
non-typhoidal Salmonella has increased dramatically since the 1980s. Sal-
monella infections usually causes a self-limited gastroenteritis, but may be
divided into five categories; gastroenteritis, enteric fever, bacteremia, local-
ized infection and a chronic enteric or urinary carrier state.

One of the most serious localized manifestations outside the gastrointestin-
al tract is vascular infection. In one study of patients with bacteremia due to
Salmonella, 25% of those who were above 50 years of age developed an endothelial infection (Cohen 1978). The most common isolated subtypes of Salmonella isolated causing MAA are Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis and Salmonella group D (Soravia-Dunand 1999, Luo 2003).

Vascular infections by Salmonella may involve any artery, but aortic infections or so called Salmonella aortitis, are much more frequent than infection of the peripheral arteries. Nearly all cases of aortitis due to Salmonella result in formation of an aneurysm. Salmonella-related aneurysms are known to have a rapid progression with risk of early rupture (Brown 1984, Johansen 1984, Hsu 2004).

Salmonella is the most common organism in East Asian MAAs, especially in Taiwan (Huang 2011), and is the second most common organism in Europe/North America. This is partly explained by its prevalence in the population and partly by its proclivity to adhere to vascular endothelium, especially if it is diseased by atherosclerosis (Soravia-Dunand 1999). There are even reports on salmonella induced MAAs in young patients free of atherosclerosis (Meerkin 1995). Marked geographical microbial differences exist with Salmonella enteritidis being more dominant in Europe, but less common in Asia, where the variety of circulating serotypes are more common. The exact mechanism of adhesion and cell invasion is not known, but endothelial cell endocytosis or phagocytosis of Salmonella has been proposed as a plausible mechanism. And that this could work in synergy with the fibronectin and promote more efficient endo-/phagocytosis (Wadström 2012). To gain more knowledge on this and to understand what makes Salmonella infect the vascular endothelium more successfully than other bacteria, isolates should be collected prospectively and analyzed regarding serotype and genome sequencing to identify characteristics in the bacteriae that cause MAA, and to compare these to a group of controls. Then experiments could be performed on vascular endothelium.

Other microorganisms

Infected aortic aneurysms caused by fungi are very rare, only seven cases have been reported between 1966 and 1999 (Parameswaran 2008) (Osler’s terminology was not entirely wrong after all). Reported cases have included Candida, Aspergillus, Cryptococcus and Paracoccidioidomycosis. In most of the cases, fungal aortitis occurred in the setting of disseminated infection, commonly involving the abdominal aorta (Muller 2001, Brown 1984, Cina 2001, Barry 1997, Cherri 1998).
Epidemiology

Incidence and Patient characteristics

There is no population-based study of the epidemiology of mycotic aortic aneurysms. In western countries the incidence have been estimated to 0.65-2.3% of all aortic aneurysms (Reddy 1991, Bandyk 1993, Muller 2001, Oderich 2001) through retrospective analysis of in-hospital or vascular surgery registries. In East Asia the reported incidences were 3-13.3% of all aortic aneurysms (Hsu 2002, Luo 2003, Kyriakides 2004, Ting 2005, Woon 2008). MAAs seem to occur more frequently in men, who constitute 75% of the cases. The patients are most often between 60 and 70 years of age, and closer to 60 in East Asian countries and closer to 70 in western (Reddy 1991, Muller 2001, Sedivy 2012, Yu 2011).

In modern materials patients have at least one cardiovascular risk factor such as hypertension, hyperlipidemia, smoking, previous stroke or myocardial infarction in 83-93% (Miller 1999, Yu 2011, Reddy 1991). An immunosuppressive state is present in 30-72%; for example diabetes mellitus, steroid treatment, renal failure, AIDS or alcoholism (Oderich 2001, Woon 2008, Yu 2011). Cardiovascular risk factors and immunosuppressive states are risk factors for MAAs in both western and Asian countries. An on-going or recent non-aortic infection can be seen in 46-100% of patients (Muller 2001, Yu 2011, Oderich 2001). MAA has been seen as a very rare side effect after BCG-treatment (Bacillus Calmette-Guerin) of superficial bladder carcinoma (Davis 2015). MAA has been seen in transplanted patients (Gerada 2013), but a systematic review of this category of patients has not yet been performed.

In short, MAA is a rare disease, typically affecting elderly subjects with an atherosclerotic aorta, and usually with an immunosuppressive state and/or on-going infection.

Prognosis

Until successful surgery was performed for the first time in 1962 all cases of MAA were invariably fatal. Today, depending on mode of surgical treatment, and thanks to advancement in intensive care and antimicrobial therapy, the 30-day survival ranges from 60-95% (Muller 2001, Oderich 2001, Jia
2013), see details under Management. MAAs with fistula formation, either enteric or bronchial, has been said to have an in-hospital mortality of 60% (Kritpracha 2011) and represents a unique entity of MAAs with an especially poor prognosis.
Diagnosis

There is no consensus on the definition of MAA or diagnostic criteria. However, it is important to distinguish primary infections of the native aorta (i.e. an MAA) from secondary aortic infections, such as graft infections, aorto-enteric fistulae (AEFs, may be primary or secondary), and inflammatory aneurysms because they are different pathologic entities and their difference in course of natural history and management.

The definition of an MAA, as an aneurysm with proven bacterial infection in the aortic wall, however, creates an inherent limitation in studies of this disease, for reasons mentioned and discussed in the Bacteriology chapter, and especially when treated endovascularly where bacterial culture from the aortic wall cannot be obtained without risk.

The diagnosis of MAA is a three legged horse, based on a combination of the following three criteria; 1) clinical presentation, 2) laboratory findings, and 3) radiological findings on computed tomography (CT) or magnetic resonance imaging (MRI). One of the mentioned criteria is solely not sufficient for the diagnosis of MAA. These criteria have evolved through the last two decades through a silent consensus in between authors studying infected aneurysms (Muller 2001, Oderich 2001, Kan 2007, Hsu 2002, Sedivy 2013). Some authors demand a positive blood culture while some do not.

Clinical presentation

In contrast to degenerative aortic aneurysms MAAs are symptomatic. The two most typical symptoms are pain and fever, in 75-100% and 56-100% respectively (Mundth 1969, Yu 2011, Reddy 1991, Jia 2013, Hsu 2004, Chan 1994, Sedivy 2012, Miller 1999, Woon 2008, Soravia-Dunand 1999). Shock from rupture is present in 9-58% (Mundth 1969, Yu 2011, Reddy 1991, Jia 2013, Hsu 2004, Sedivy 2012). Patients often also present with sepsis and/or concomitant infections e.g. psoas abscess, tachycardia, hypotension and local symptoms depending on the site of the aneurysm e.g. hemoptysis, Ortner’s syndrome and dysphagia aortica. Symptoms may develop very fast, from one day to another, or in rare cases over several months. In the latter situation symptoms such as fatigue, malaise, weakness, or weight loss may be the most prominent (Miller 1999, Soravia-Dunand 1999). Hence, there is no pathognomonic symptom for this very rare disease. In the literature one may
encounter a so-called symptomatic triad of MAA including abdominal pain, fever and a pulsatile, rapidly growing abdominal mass.

Laboratory findings

Inflammatory markers are often elevated C-reactive protein (CRP) is elevated in 47-76.5% and 45-72% have leukocytosis (Miller 1999, Sedivy 2012, Woon 2008, Chen 2005, Reddy 1991, Clough 2009). Procalcitonin has so far not been evaluated in this setting. Cultures are positive in 50-75% of cases, see *Bacteriology* for details (Fillmore 2003, Muller 2001, AbdelAzim 2005). 16srRNA or broad range PCR and DNA sequencing could be an assisting diagnostic tool to determine bacteriologic agent in case of negatives cultures.

Radiological findings

Radiological findings on computed tomography (CT) or magnetic resonance imaging (MRI) include: loss of intimal calcification, saccular aneurysm, multilobular aneurysm, eccentric aneurysms with narrow neck, rapid expansion, periaortic and intrathrombus gas formation, and periaortic soft tissue mass (Macedo 2004, Atlas 1984, Wilde 1987, Gonda 1988, Mantello 1990, Lee 2008). Early changes of aortitis preceding aneurysm formation include an irregular arterial wall, periaortic edema, a periaortic soft-tissue mass, and periaortic gas (Lee 2008). The most common finding is a peri-aortic mass, and is found in 48% of cases (Lee 2008), which combined with a saccular-shaped aneurysm is a key feature. As opposed to uninfected aneurysms, calcification within the aneurysm wall is uncommon in infected aneurysms.

MRI may prove helpful where contrast media are contraindicated. Positron emission tomography CT (PET-CT) with fluorodeoxyglucose (FDG) as tracer may serve as a good complementary diagnostic instrument when recurrent infection complications to treatment are suspected (Legout 2012).

Transoesophageal echocardiography (TEE) has the advantage of being possible to perform bedside in an emergency setting, but cannot visualise the distal part of the ascending aorta, and its capacity to evaluate cross-sectional dimensions of a tortuous aorta is limited (Zamorano 2003).
**Figure 3.** MAA on computed tomography located in the lower descending part of the aorta stretching down in the upper abdominal part.
Management

MAAs were described as being invariably fatal by Bennet et al in 1967. Medical therapy alone has a mortality of nearly 100% (Oskou 1993, Wang 1996, Chan 1995), although spontaneous healing has been reported anecdotally (Johansen 1980). It has been concluded that treatment for MAA must be a two-edged sword comprising; prompt surgical intervention and immediate administration of systemic antibiotics. Successful resolution relates to early diagnosis and expedient treatment. Despite lack of evidence, gold standard is open surgical repair (OR); with resection of the aneurysm, extensive local debridement, and revascularisation by in-situ reconstruction or extra-anatomic bypass. The anatomical location of the aneurysm sometimes makes surgical repair very demanding, or even impossible.

The last 15 years has seen a boost in reports on successfully treated MAAs with endovascular aortic repair (EVAR). Major concerns regarding not resecting the infected tissue, including the aneurysm itself, and the risk of recurrent/persistent infection have been raised and EVAR has therefor been regarded with sceptisism. The major advantages highlighted with endovascular approach are: enabling treatment of old comorbid patients with challenging aneurysm anatomy, avoidance of large incision, full heparinization, cardiopulmonary bypass, aortic crossclamping, impairment of respiratory function, and massive blood transfusion.

No reliable comparative data exists between OR and EVAR.

Open surgical treatment

Extra-anatomic reconstruction

The entire aneurysm is resected, the infected tissues are debrided, drainage may be established and arterial reconstruction is performed by axillofemoral bypass through uninfected planes. Its primary advantage being avoidance of graft placement in infected fields. The procedure has three major disadvantages; the proximal aorta – the aortic arch, thoracoabdominal aorta and paravisceral aorta - is not amenable to extra-anatomic reconstruction, the procedure is time-consuming and carries considerable risk of early and late complication. Extra-anatomic bypass was the operation of choice during the 1970s and 1980s, but showed discouraging complication numbers with 20%
aortic stump disruption, 20-29% amputation rate and a 20% risk of reinfection (Éwart 1983). In a large multicenter study early mortality was 24% and primary patency at two years 62%. Eight percent were complicated by aortic stump ruptures and seven percent by infection (Bacourt 1992). In a more recent study of 18 patients the disease-specific mortality was 39% (Woon 2008).

Even if the last two decades have seen a decline in the use of this procedure due to high complication rates, it will remain an important alternative approach in the surgical arsenal for MAA.

**Figure 4.** Extra-anatomic reconstruction for MAA.

*In situ reconstruction*

The entire aneurysm is resected, the infected tissues are debrided until a healthy artery is present to which an anastomosis can be made. Drainage if necessary and direct arterial reconstruction is performed. Options for conduit include femoral-popliteal vein (NAIS, Neoaortoiliac system), cryopreserved homografts and prosthetic grafts with or without antibiotic or antibacterial impregnation. Once arterial reconstruction is performed it is usually covered
with a viable omental flap. In contrast to the extra-anatomic approach in situ reconstruction is feasible in most aortic sites. The main concern is of graft infection, since the conduit is placed in a contaminated field.


Uchida et al published their experience with a rifampicin-bonded graft as conduit with coverage with omental pedicle grafting, including reconstruction of the thoracic aorta. A total of 23 patients were operated on with this technique between 2003 and 2010, with only one in-hospital death and an overall 95% survival at 5 years (Uchida 2012).

In the 1990s small reports on successful treatment with cryopreserved arterial allografts as conduit (Knosalla 1996, Vogt 1998) were published. The potential benefit of this technique is resistance to reinfection, but difficulties to obtain and store the allograft are disadvantages. Concerns have also been raised after a recent large study showed a mortality of 39% at one year and a graft-related complication rate of 19% (Touma 2014).

An alternative conduit could be autologous vein, so called NAIS, neoaortoiliac system. Replacement with deep vein, femoro-popliteal vein, as conduit has the advantage of being resistant to infection, but the disadvantage of long operative times and increased morbidity. The former, which might be overcome by a 2-team approach, reduces operative times with 50%. NAIS has a reported 30-day mortality rate of 7.5% and an assisted primary patency at 1 year of 100%, however not for MAA specifically but miscellaneous pathologies (Beck 2008, Budtz-Lilly 2014).
Endovascular treatment

All cases where the infected aneurysm is treated with an endovascular device and thus leaving the infected nidus in situ are considered endovascularly treated, thus also including MAAs treated with hybrid repair (combination of endovascular and open repair). Placing a foreign body in an infected field goes against traditional surgical principals, and therefore the acceptability of EVAR is controversial. The idea is that early and broad-spectrum ABx might eliminate or suppress the bacterial focus, and because the endoprosthesis is located in the aorta steeped by antibiotic loaded blood, the antibiotics may also permeate through the graft fabric and continue to act against the infected aortic wall after surgery. However, no study has been performed to support this theory of antibiotics permeating through the graft.

The major advantages with endovascular approach are: minimally invasive enabling treatment of old, comorbid patients with challenging aneurysm...
anatomy, avoidance of an anastomosis in an infected field with the risk suture insufficiency or aneurysm development. EVAR has by some, been suggested to serve as a bridge to later open surgery allowing the patient to recover from a state of sepsis/circulatory shock and by others to be a palliative or definite form of treatment (Kan 2007, Razavi 2008, Clough 2009).

Reports on EVAR for MAA show promising results but only small single centre case-series with limited follow-up have been published, the first was by Semba in 1998 (Sedivy 2012, Kan 2010, Jones 2005, Clough 2009, Semba 1998, Jia 2013, Tsai 2013, Kritpracha 2011, Razavi 2008). A review of 48 cases from 22 reports found a 30-day survival rate of 89.6%, and a two-year survival rate of 82.2% (Kan 2007). The largest serie to date, by Sedivy et al comprising 32 MAA-patients, had three (11.5%) late infection-related deaths. The rates of endoleakage seem underreported in these materials, or are actually low due to the fact that most MAAs are saccular making type I-, II-, and III- leakages less likely.

As long as the crucial questions of durability, risk of severe recurrent infections and long-term survival are unanswered the role of endovascular surgery for MAA will remain undefined. There is a risk that the existing, small positive reports may represent a positive selection. At the time of writing this, there is no report on endovascular aneurysm sealing, EVAS, for MAA.

Figure 6. A stentgraft excluding a thoracic MAA, right hand picture is zoomed-in.
Antibiotics

Solely antibiotic therapy (ABx) for MAA had a reported mortality of nearly 100% before the 1990s (Oskoui 1993, Wang 1996, Chan 1995, Hsu 2004). In 2009 Hsu published 22 cases treated with antibiotics only, which were considered too high risk for surgery, and concluded that 1-year survival was 68% (Hsu 2009), hence some MAAs might heal with antibiotics only but the risk of rupture or recurrence in disease is unknown.

Intravenous antibiotic therapy should be commenced as soon as the diagnosis is suspected. Some review articles of endovascular therapy propose favourable outcome with delayed surgery with initial ABx for one week in circulatory stable patients. The point is to eradicate bacteria from the aorta and bloodstream before deploying a body-foreign stentgraft (Kan 2007, Kan 2010). One Taiwanese centre delays OR four to six weeks for the benefit of ABx in non-urgent cases (Hsu 2002), with very good results. Postoperatively the duration and choice of ABx is an important matter of debate with no consensus in the literature. In case of open surgery the time of postop ABx would reasonably be much shorter than if treated with endovascular approach. In Taiwan where the incidence of MAA seem highest and the clinical experience would be expected to be greatest, there are two centres – one which mainly perform open and one endovascular surgical repair - treat their patients with intravenous ABx for four to six weeks post-surgery and/or until fever subsides and inflammatory markers are normalized, and then continued with oral ABx for at least six to twelve months, and in some cases life-long (Hsu 2004, Kan 2007, Kan 2012). However, long-term ABx puts the patient at risk of adverse drug reactions and possible acquisition of resistant organisms, and the problem of compliance increases.

Adjunctive procedures

In case of EVAR some authors have been aggressive in the use of adjunctive therapies e.g. percutaneous drainage of the aneurysm sac or periaortic abscess, open debridement and reconstruction, and application of saline and antibiotic irrigation (Jia 2013, Tsai 2013, Oshima 2014). Whether these adjunctive measures have a role in the management of MAAs treated endovascularly is, however, unclear. It is possible that it may help in selected cases; if not, CT-guided drainage would offer additional culture information, which might help determine further treatment strategy. In some cases open deviations are needed as adjunctives to endovascular surgery e.g. bypass of visceral, femoral or neck vessels.

In the 1970s some recommended routine cholecystectomy to eliminate a microorganism pool and reduce risk of recurrence (Wilson 1978, Ewart
1983), the benefits of this is unclear and the adjunct procedure is rarely performed nowadays.

Risk factors for adverse outcome and persistent infection

Since all existing reports on MAA are small, it has not yet been possible to demonstrate robust statistically significant risk factors for aneurysm-related death and persistent infection. However, some analysis have been performed and for OR those who have been stated as statistically significant in published articles have showed advanced age, non-*Salmonella* infection and no surgery as independent risk factors for aneurysm-related death (Hsu 2004, 46 patients), extensive periaortic infection, female gender, *S aureus* infection, rupture, and suprarenal location (Oderich 2001, 43 patients), and suprarenal location again (Yu 2011, 56 patients).

After EVAR for MAA the literature review by Kan in 2007 showed in a multivariate logistic regression analysis rupture and fever at the time of surgery as predictors for persistent infection (Kan 2007, 48 patients).
Other infected arterial aneurysms

Infected aneurysms occur not only in the aorta, but also in peripheral arteries, cerebral arteries and visceral arteries in descending order (Charlier 1988, Lee 2008). In conformity with MAAs, infected aneurysms of other arteries are dominantly caused by bacteria. Infected peripheral aneurysms of the femoral artery or the arm are mostly caused by trauma, intra-arterial drug injection or iatrogenic interventions. Engagement of the popliteal and carotid arteries are extremely rare and most often the result from septic embolization from infective endocarditis. Intracranial infectious aneurysms represent 0.7-5.4% of all intracranial aneurysms (Nakahara 2006), and the most common source of infection are infective endocarditis, 65%, but also bacterial meningitis and poor dental hygiene (Ducruet 2010). Infected aneurysms of the visceral arteries are beyond rare, but when present they most often appear in the superior mesenteric artery, and secondly in the celiac artery and its branches (Rutherford 8th edition).

Infected arterial aneurysms do not exclusively affect the elderly. There are several reports on development of infected aortic aneurysms in children and even neonates whom have either undergone umbilical artery catheterization or intervention for coarctatio of the aorta (Khazei 1967, Bergsland 1983, Cribari 1992, Baillie 2000, LeNoir 2015).

As a curiosity it can be mentioned that mycotic aneurysms have also been diagnosed in other species, such as monkeys, dogs and horses (Okamoto 2007, Sharma 2011, Gershenson 2011).
Open abdomen

Open abdomen, OA, treatment is applicable in multiple surgical settings. It may serve as a preventive and therapeutic measure in the septic abdomen, the tense abdomen after resuscitation, in damage control situations, or to treat the abdominal compartment syndrome (ACS) (Rotondo 1993, Björck 2009, Mayer 2010).

Definitions

Intra-abdominal pressure (IAP) is usually measured through a catheter in the urinary bladder and is expressed in millimetres of mercury (mmHg). It should be measured at end-expiration in supine position after ensuring relaxation of the abdominal muscles (Björck 2008). IAP is normally subatmospheric to 0 mmHg. Intra-abdominal hypertension (IAH) is defined, according to the World Society of the Abdominal Compartment Syndrome (WSACS) (Malbrain 2006), by a sustained or repeated pathological elevation of IAP ≥12 mmHg, and is graded as follows:

- Grade I: IAP 12-15 mmHg
- Grade II: IAP 16-20 mmHg
- Grade III: IAP 21-25 mmHg
- Grade IV: IAP > 25 mmHg

ACS is defined as IAP ≥ 20 mmHg measured at least twice, with newly developed organ dysfunction or failure (Björck 2014).

Pathophysiologic effects of IAP elevation

A normal IAP in a critically ill patient is 5-7 mmHg, and starting from 12 mmHg the pressure has a negative impact on several organ functions (Malbrain 2006) of the body; With an increase in IAP, the diaphragm rises, causing elevation of intra-thoracal pressure thus obstructing venous return, which may lead to increased risk of deep vein thrombosis, pulmonary emboli, affects cardiac output and may yield ventilator problems. A secondary effect of increased intra-thoracal pressure is reduced cerebral perfusion,
which might manifest in encephalopathy. The liver, kidneys and intestines are mainly affected through reduced perfusion causing hypoxic necrosis in the liver, anuria, and intestinal ischemia/gangrene with translocation of intestinal bacteria (Vivier 2006, Bloomfield 1997, Schachtrupp 2010, Ivatury 1998, Kirkpatrick 2015).

Incidence of IAH/ACS after aortic surgery

IAH and ACS are common and potentially serious complications in patients with ruptured abdominal aortic aneurysms (rAAA) repair. The incidence of ACS after OR of rAAA is about 30% and approximately 20% after EVAR (Björck 2010, Björck 2014, Rubinstein 2015, Karkos 2014, Ersryd 2016).

If ACS is untreated the mortality is near 100%, and if treated between 30-70% (Mayer 2009). Risk factors for IAH/ACS when performing surgery of AAA are peri-operative bleeding > 5 litres for rAAA and iAAA, low blood pressure pre-operatively, use of aortic occlusion balloon and unconsciousness for rAAA, and reimplantation of renal artery in iAAA (Ersryd 2016).

Management of IAH/ACS

A high index of suspicion and/or routine measurement of IAP in intensive care unit patients is warranted so the condition can be recognized as early as possible and treatment initiated. Treatment can be divided in two categories: non-surgical and surgical.

Non-surgical therapy. Non-surgical therapy consists of five therapeutic interventions: evacuation of intraluminal contents (nasogastric or rectal tube, colonoscopic decompression or pharmacological decompression), evacuation of intra-abdominal space-occupying lesions (percutaneous drainage), improve abdominal wall compliance (neuromuscular block or anesthetics), optimize fluid administration and regional tissue perfusion (hypertonic solutions and colloids, in combination with furosemide) (Cheatham 2009, Björck 2014).

Surgical therapy. If conservative methods are unsuccessful and IAP is >20 mmHg and ACS develops, a decompression of the abdomen is necessary and life-saving (Chen 2008). Decompression laparotomy is performed through a complete mid-line incision with an instant fall in IAP (De Waele 2006), and an immediate effect is seen on organ function with improved oxygenation and urinary output (De Waele 2016). Afterwards temporary abdominal closure is needed. Several techniques have been developed, aiming to allow abdominal closure as soon as possible without compromising the patient's physiologic condition.
OA as a concept

The purpose of OA is obviously to decrease IAP to normal and alleviate its harmful consequences, in order to let organ dysfunction recuperate. The aim is to close the abdomen as soon as possible, because OA is also a very morbid procedure. Several techniques of temporary abdominal closure (TAC) have been described: skin only closure, Bogota bag, meshes, sheets, zippers, slide fasteners, sandwich technique, Wittman patch, retention sutures, vacuum pack, and vacuum assisted wound closure (VAWC), with or without mesh mediated fascial traction (Boele van Hensbroek 2009). The chosen OA technique must prevent adhesions between the intestines and the bowel, lateralisation of the bowel wall and contamination, thus permitting an early closure, which is the most important factor to avoid complications (Björck 2009). The longer the duration of OA treatment, the greater the risk becomes of developing serious complications such as entero-atmospheric fistulae (EAFs) and other infections. In younger patients, predominantly suffering from trauma, fascial closure of the OA within 1 week is often possible (Suliburk 2003). In elderly patients undergoing treatment of OA after aortic aneurysm (AA) repair a longer duration might be required, and therefore a different technique is warranted in this subgroup of patients.

OA and the risk of vascular infection

The longer the duration of OA treatment, the greater the risk becomes of developing serious infections, which hence might engage the vascular system, e.g. graft infections and AEFs. The actual risk of developing vascular infections after OA is, however not known. The reported incidence of bloodstream infection in ICU patients with IAH is 21% (Vidal 2008). There are six publications evaluating temporary abdominal closure devices after AA repair in the literature, and there has only been one case of graft infection reported. However, most of them are retrospective and small, and have used different OA techniques (Barker 2007, Petterson 2007, Ross, 2009, Mayer 2009, Kimball 2009, Seternes 2010).
Aims of thesis

The overall aim of the thesis was to investigate aspects of treatment for MAAs, in particular endovascular treatment and long-term outcome, and the risk of aortic infection after OA treatment.

Specific aims:
To study short- and mid-term outcome after EVAR for MAA.

To study the durability of EVAR for MAA, by assessing the late infection-related complications and long-term survival.

To study short- and long-term survival after MAAA repair with open and endovascular technique.

To study rate of recurrent infections and reoperations after MAAA repair with open and endovascular techniques.

To study time-trends in surgical treatment of MAAA.

To evaluate vacuum-assisted wound closure and mesh-mediated fascial traction (VACWM) after treatment with open abdomen in patients treated for aortic aneurysm, by assessing late complications, in particular graft infections, EAFs and incisional hernias.
Patients and Methods

Definition of MAA/MAAA

An MAA/MAAA was defined in paper I-III as a combination of the following 3 criteria: (1) clinical presentation (pain, fever, sepsis, or concomitant infection), (2) laboratory tests (elevation of inflammatory markers like C-reactive protein and white blood cells, or positive cultures), and (3) radiological findings on computed tomography (CT) or MRI (rapid expansion of aneurysm, saccular aneurysm, multi-lobular aneurysms, eccentric aneurysms, periaortic gas, and periaortic soft tissue mass).

Patients and methods

**Paper I.** All patients treated for MAA at Uppsala University Hospital between January 2000 and December 2007 were identified by scrutinizing four different data sources: The SWEDVASC registry, the registry of the Radiological Department, the In-Patient Registry of the University Hospital, and a specific list updated continuously by the investigators. Case records were reviewed retrospectively. Patients were assessed postoperatively with a clinical examination, hematologic tests, and imaging at 1, 6, and 12 months, and then annually thereafter. If a complication was suspected, more frequent evaluations or reinterventions were performed. Postoperative imaging was primarily performed with CT, but could be replaced with ultrasound (US) imaging in infrarenal aneurysms with no clinical sign of reinfection. In case of suspected graft infection, 18-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) was performed. Survival data were obtained from the Swedish national population registry in July 2008.

**Paper II.** All patients treated endovascularly for MAAs at 16 European centres from eight countries between 1999 and 2013 were identified. Case records were then retrospectively reviewed through a common study protocol, see appendix.
Figure 7. Map of Europe marking centers participating in paper II.

Paper III. All patients treated in Sweden for MAAAs 1994-2014 were identified in the Swedish vascular registry. All 27 vascular units in Sweden participated in retrieving data by a retrospective chart review according to a predefined protocol, and survival was cross-matched with the population registry. The cohort was divided in three time periods (1994-2000, 2001-2007, and 2008-2014), and data were analysed regarding changes in treatment strategy and outcome over time. Incidence of MAAA repair was assessed as proportion of all abdominal aortic aneurysm (AAA) repairs registered in the Swedish vascular registry. Comparative analysis was performed for the first 90-days and 1-year after surgery as short-term outcome, and long-term outcome at the intervals of 5-years and 10-years of MAAA repair based on treatment strategy.

Paper IV. A multicentre prospective study was performed including all consecutive patients treated with OA at four Swedish centres (Falun, Gävle, Malmö and Uppsala) between April 2006 and August 2009 (Acosta 2011). Paper IV was a subgroup analysis of the patients treated with OA with VAWCM after operation for aortic aneurysm, AA. All surviving patients underwent a 1-year follow-up examination with clinical assessment as well as with a computed tomography (CT) of the abdomen to detect late complications.
Statistics

Data was assessed for normality with histograms. Continuous variables were given as mean (±SD) or median (range), and categorical variables as proportions (%). For comparisons between groups different tests were used for parametric/non-parametric, continuous or categorical data. For all two-tailed statistical tests a p<0.05 was considered statistically significant. For survival analysis the Kaplan-Meier method was used, and for testing group differences log rank-test was performed. Statistical evaluations of the data in all four studies were performed with a computer software package (SPSS, Chicago, IL, USA), and additional statistical analyses in paper II and III for calculation of competing risk and propensity weighted analysis by using R\textsuperscript{14} (Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Some additional statistical analyses were performed in:

**Paper II.** Univariable Cox regression risk factor analyses were performed. In the risk factor analysis the microbiological cultures were divided in three subgroups; negative, Salmonella positive and non-Salmonella positive cultures (all others). The cumulative incidence of infection-related death accounting for the competing risk of death of other causes, and the cumulative incidence of re-intervention (open and/or endovascular) with the competing risk of all-cause death, was calculated. The competing risk analysis was performed by a statistical consultant.

**Paper III.** Univariable and multivariable logistic regression (for perioperative mortality) and Cox regression (for long-term mortality) analyses were performed, and odds/hazard ratios were calculated as estimates of relationships between investigated predictors and outcome. Factors with a p-value <0.2 in the univariable analysis were included in a forced-entry multivariable analysis. For comparison of OR and EVAR, sensitivity analysis was performed with propensity score weighted correction for patients treated with each operative technique. To assess difference between OR and EVAR regarding infection-related death a competing risk analysis was performed. The competing risk and propensity weighted analyses were performed by a statistical consultant.
Results

**Paper I.** Eleven patients underwent endovascular repair of 13 MAAs between 2000 and 2007. Eight of the MAAs had a suprarenal location, and five were in the infrarenal abdominal aorta. Mean follow-up was 27 months. The 30-day survival was 91%, and 73% at 1-year. A bleeding aorto-esophageal fistula resulted in one in-hospital death <30 days. Three patients died later: one each of sepsis, stent migration that caused intestinal ischemia, and one of unknown cause. Two patients had recurrent sepsis postoperatively but no vascular complications, two had elevated inflammatory markers during follow-up but were asymptomatic, and three patients had an uneventful follow-up.

**Figure 8.** Paper I, Kaplan-Meier curve demonstrating postoperative survival.

*Comment:* Only one patient was operated with OR at Uppsala 2000-2007.
Paper II. 123 patients with 130 MAAs were identified. Mean age was 69 years (range 39-86), 87 (71%) were men, 58 (47%) had some immunodeficiency, and 47 (38%) presented with rupture. Anatomical locations were; ascending/arch (n=4), descending (n=34), paravisceral (n=15), infrarenal aorta (n=63), and multiple (n=7). Treatments were; thoracic EVAR (n=43), fenestrated/branched EVAR (n=9), and infrarenal EVAR (n=71). Antibiotic was administered for a mean time of 30 weeks. Mean follow-up was 35 months (range 1 week-149 months). Six patients (5%) were converted to open repair during follow-up. Survival was 91% (95% CI 86-96%), 75% (67-83%), 55% (44-66%), and 41% (28-54%) after 1-, 12-, 60-, and 120-months, respectively. Infection-related complications after EVAR for MAA occur in 27% of the patients, of whom 70% died (19% of the total cohort). A Cox regression analysis demonstrated non-Salmonella positive culture as predictors for late infection-related death.

Figure 9. Paper II, a Kaplan-Meier 10-year survival curve of 123 patients treated for MAA with endovascular technique.
**Table 4.** Paper II, Univariable Cox-regression analysis of long-term mortality.

<table>
<thead>
<tr>
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<th>No. Of Deaths / Total No With the Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
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<td>Age</td>
<td>-</td>
<td>1.0 (1.1-1.1)</td>
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<td>Male sex</td>
<td>34/87</td>
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<td>1.7 (0.5-5.6)</td>
<td>0.357</td>
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<td>COPD</td>
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<td>0.9 (0.4-2.0)</td>
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<td>3/13</td>
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<td>24/57</td>
<td>1.0 (0.6-1.8)</td>
<td>0.897</td>
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<td>C-reactive protein</td>
<td>-</td>
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<td>Rupture</td>
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<td>Periaortic soft tissue mass</td>
<td>28/61</td>
<td>1.2 (0.7-2.1)</td>
<td>0.517</td>
</tr>
<tr>
<td>Revascularization of branches</td>
<td>8/20</td>
<td>1.4 (0.6-2.9)</td>
<td>0.433</td>
</tr>
<tr>
<td>Length of aorta covered (cm)</td>
<td>-</td>
<td>1.0 (0.9-1.0)</td>
<td>0.444</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease, HR hazard ratio.

**Comment:** The reviewers advised against performing multivariable Cox-regression analysis in order to avoid multiple testing.
Figure 10. Paper II, Kaplan-Meier curves for different subgroups. Nota bene, the left lower figure showing non-Salmonella positive culture survival curve.

**SUPPLEMENTAL MATERIAL**

![Kaplan-Meier curves for different subgroups](image)

*Figure 1. Kaplan-Meier survival curves for different subgroups.*

**Comment:** These analyses were published as supplemental material in the publication for *Circulation*.

**Paper III.** A total of 132 patients with 144 MAAAs were identified, (0.6% of operated abdominal aortic aneurysms). Median age was 70 years (SD 9.2),
51 were immunosuppressed, and 50 presented with rupture. Overall survival at 3-months was 86% (95% CI 80-92%), 1-year 79% (72-86%), 5-years 59% (50-68%), and 10-years 39% (27-51%).

The preferred operative technique shifted from OR to EVAR after 2001 (proportion EVAR 1994-2000 0%, 2001-2007 58%, 2008-2014 60%). Open repair (OR) was performed in 62 patients (47%); aortic resection and extra-anatomical bypass (n=7), in-situ reconstruction (n=50), patch plasty (n=3); two died intra-operatively. EVAR was performed in 70 patients (53%); standard EVAR (n=55), fenestrated/branched EVAR (n=8), visceral deviation and stentgrafting (n=7). The EVAR cohort had a lower proportion of patients with preoperative hypotension, and a higher proportion of patients of rapid aortic expansions. In a Kaplan-Meier analysis and log rank test, 3-months survival was lower for OR compared with EVAR (74.2% vs 95.7%, p<0.001), and 1-year (72.5% vs 83.9%, p=0.054), but not thereafter. During follow-up (median OR 36 months, EVAR 41 months) there was no difference in incidence of infection-related complications (OR 18%, EVAR 24%, p=0.439) or reoperation (OR 21%, EVAR 24%, p=0.650).

**Figure 11.** Paper III, number of MAAA cases/year treated with OR and EVAR in Sweden.
**Figure 12.** Paper III, Kaplan-Meier 10-year survival curve comparing OR and EVAR with propensity score weighted estimates of survival.

![Kaplan-Meier Survival Curve](image)

**Comment:** This propensity score weighted analysis was performed based on fifteen covariates (age, sex, comorbidities, patient characteristics at presentation, aneurysm characteristics, blood culture results and year of surgery). A multivariate analysis showed OR as a significant seven-fold risk factor for death at 3-months. In a multivariable Cox-regression analysis of 5-years mortality, increased age, rupture, and suprarenal aneurysm location resulted in an increased hazard ratio for death, while postoperative antibiotic treatment >6 months had a hazard ratio below 1.0.

**Paper IV.** Among 1041 patients treated with open or endovascular repair of AA at the four sites, 28 (2.9%) had OA treatment with VAWCM; another two had VAWCM after hybrid operations for thoraco-abdominal AA. Eighteen (60%) were operated on for rupture and 12 (40%) electively. Eight had suprarenal or thoraco-abdominal aneurysms. Eight (27%) died within 30 days, none due to OA-related complications. Four died before abdominal
closure; primary delayed fascial closure was achieved in all survivors. One-year mortality was 50%. Ten (33%) had bowel ischaemia requiring bowel resection.

Late potential OA-related infectious complications occurred in five (17%), all of who first developed intestinal ischaemia: entero-atmospheric fistulae (two), graft infections (two), aorto-enteric fistula (one). 1-year follow-up with clinical evaluation and CT showed no signs of graft infection. Incisional hernias occurred in 9 of 15 patients (60%); only three were symptomatic.

**Table 5.** Paper IV, table demonstrating all infectious complications after aortic surgery and OA treatment.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Indication of aneurysm repair</th>
<th>Procedure</th>
<th>Graft related infection and time after OA</th>
<th>Treatment of graft related infection</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AAA</td>
<td>EVAR</td>
<td>EAF day 15</td>
<td>Drainage with OA</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>TAAA</td>
<td>Hybrid</td>
<td>EAF day 30</td>
<td>Drainage with OA</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>rAAA</td>
<td>EVAR</td>
<td>Graft infection day 240</td>
<td>Percutaneous drainage + Abx</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>rAAA</td>
<td>EVAR</td>
<td>Graft infection day 25</td>
<td>Percutaneous drainage + Abx</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>rAAA</td>
<td>OR</td>
<td>AEF day 30</td>
<td>EVAR + Abx</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Comment:** All patients with infectious complications had previously been treated with OA after relaparotomy for intestinal ischemia.
Conclusions

Surgical management for MAA and MAAA
Short-term outcome for endovascular repair of MAA is good, 91% survival at 30-days, with acceptable mid-term survival, 73% at 1-year.

Long-term outcome for endovascular repair of MAA is relatively good, 55% survival at 5-years and 41% at 10-years.

Infection-related complications after EVAR for MAA occur in 27% of the patients, of whom 70% die. These infection-related complications mostly occur during the first postoperative year. A non-Salmonella positive culture is a predictor for late infection-related death.

Endovascular treatment of MAA is feasible and for most patients a durable treatment option. Late infection-related complications do occur and are often lethal, and warrant long-term antibiotic treatment and follow-up.

Short-term outcome for OR of MAAA is at 90-days 74% survival and at 1-year 73%, and for EVAR 96% and 84% respectively. The difference in survival between OR and EVAR is significant at 90-days (p<0.001), but not thereafter.

Long-term outcome regarding survival for OR of MAAA is at 5-years 60% and at 10-years 39%, and for EVAR 58% and 41% respectively.

There is no difference in rate of recurrent infection or reoperation between OR and EVAR in Sweden.

After year 2001 a paradigm shift in treatment of MAAA occurred in Sweden, with EVAR being the preferred treatment modality.

OA after AA-repair
VAWCM provides a high fascial closure rate after AA-repair and long-term OA treatment.
Infectious complications, such as graft infections occurred after intestinal ischaemia and prolonged OA treatment (2/30).

Asymptomatic incisional hernias were common after treatment with OA and VAWCM.
General discussion

At the start of this thesis, several questions regarding MAAs and OA were identified. The following three issues were the most important:

1. Revised definition, uniform terminology and criteria for the diagnosis of MAA, aortic graft infection and aorto-enteric fistulae are absent and need to be defined. It is also important to reach a broad acceptance for such criteria. This would facilitate research and elevate the level of knowledge of MAA.

2. Is EVAR for MAA a durable option of treatment? If so, treatment might be offered to more patients with a more challenging anatomy and severe comorbidity. It would be valuable to compare outcome of open and endovascular surgical treatment of MAAs, regarding survival and recurrence of infection. To answer this, a multicentre or nationwide study would need to be performed to gather as many cases as possible because of the rareness of the disease.

3. What is the risk for late aortic infection after prolonged OA-treatment after AA-repair, in particular graft infection?

Limitation of thesis

In short the limitations consist of; Confusing terminology, small sample case series/cohorts with risk of selection bias, risk of missing data due to retrospective study design, risk of selective loss to follow-up, risk of confounding low-powered statistical analysis, and lack of comparative analysis.

Limits in definition and methods

An obstacle performing research on MAA and making comparative analysis is the absence of an international consensus on the definition, terminology and diagnostic criteria of MAA, see table 6.
**Table 6.** A summary of different terminologies, definitions and classifications of MAA. *Indicates unclear definition and diagnostic criteria.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Terminology</th>
<th>Definition/diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osler, 1885</td>
<td>Mycotic aneurysm</td>
<td>Aneurysm associated with infective endocarditis</td>
</tr>
<tr>
<td>Eppinger, 1887</td>
<td>Embolomycotic</td>
<td>Infectious and embolic etiology of aneurysm</td>
</tr>
<tr>
<td>Wiesel, 1906</td>
<td>-</td>
<td>Not all aneurysms due to infection are related to endocarditis, but to infection in general</td>
</tr>
<tr>
<td>Lewis, 1909</td>
<td>Embolomycotic aneurysm</td>
<td>Causes of aneurysm due to infection were not solely endocarditis but also trauma and other infection</td>
</tr>
<tr>
<td>Crane, 1937</td>
<td>Primary mycotic aneurysm</td>
<td>Aneurysm developed with no associated intravascular focus, no intra-extra vascular inflammation or endocarditis</td>
</tr>
<tr>
<td>Blum, 1962</td>
<td>Cryptogenic mycotic aneurysm</td>
<td>Bacteria invading the endothelium at the site of atherosclerotic disease</td>
</tr>
<tr>
<td>Jarrett, 1975</td>
<td>Infected aortic aneurysm</td>
<td>Objecting the term mycotic, since indicating a fungal genesis</td>
</tr>
<tr>
<td>Patel, 1977</td>
<td>Mycotic aneurysm</td>
<td>Switch of terminology, consider pre-existing arterial status and source of infection, excluding infected pre-existing aneurysms, intracranial aneurysms and infected prostheses</td>
</tr>
<tr>
<td>Wilson, 1978</td>
<td>Spontaneous arterial infections</td>
<td>Spontaneous arterial infections, classification and subgroups: mycotic aneurysms, infected aneurysms, microbial arteritis, traumatic infected pseudoaneurysm</td>
</tr>
<tr>
<td>Oz, 1989</td>
<td>Bacterial aortitis</td>
<td>Emphasizes that aortas of normal diameter may be infected</td>
</tr>
<tr>
<td>Chan, 1989</td>
<td>Mycotic aneurysm of the aorta</td>
<td>*Naturally occurring aortic aneurysms that result from or are secondarily infected by bacteria arising in a distant site of infection</td>
</tr>
<tr>
<td>Reddy, 1991</td>
<td>Infected aortoiliac aneurysm</td>
<td>Retaining Wilson's classification, and adding a subgroup of aortic infection due to contiguous spread from adjacent organ</td>
</tr>
<tr>
<td>Sessa, 1997</td>
<td>Infected aneurysm</td>
<td>*A lesion of the arterial wall due to bacterial contamination</td>
</tr>
<tr>
<td>Müller, 2001</td>
<td>Mycotic aneurysm</td>
<td>Positive culture from aneurysm wall/content/surrounding tissue, and signs of infection. If negative culture, aneurysm is mycotic only if 1) intraoperatively typical aspects, 2) Clinical signs of infection and 3) Treated with antibiotics before surgery</td>
</tr>
<tr>
<td>Oderich, 2001</td>
<td>Infected aortic aneurysm and primary aortic infection</td>
<td>Operative findings, clinical infection, and positive aneurysm culture</td>
</tr>
<tr>
<td>Luo, 2003</td>
<td>Septic aortic pseudoaneurysm</td>
<td>Aortic pseudoaneurysm caused by infection with or without bacteremia, excluding fusiform aneurysms</td>
</tr>
<tr>
<td>Jones, 2004</td>
<td>Mycotic aortic aneurysm and infected false aneurysm</td>
<td>*No definition. Including aorta-branchial, aorto-esophageal and aorto-cutaneous fistulae, which had previous thoracic aortic grafts.</td>
</tr>
<tr>
<td>Kyriakides, 2004</td>
<td>Mycotic aortic aneurysm and primarily infected aortic aneurysm</td>
<td>*Unclear definition, however excluding prosthetic graft infections, arterial infection secondary to trauma and aneurysms with positive routine culture</td>
</tr>
<tr>
<td>Hsu, 2004</td>
<td>Primary infected aortic aneurysm</td>
<td>Clinical signs of infection, periaortic soft-tissue infiltration on CT or MR, aortic aneurysm &gt; 3cm, must have positive culture (blood or tissue)</td>
</tr>
<tr>
<td>Kuniyoshi, 2005</td>
<td>Mycotic aortic aneurysm</td>
<td>*Aneurysm morphology or intraoperative findings</td>
</tr>
<tr>
<td>Chen, 2005</td>
<td>Mycotic aortic aneurysm</td>
<td>*Positive culture from the aneurysm wall, or pus surrounding the aneurysm if negative culture from the aneurysm</td>
</tr>
<tr>
<td>Tiesenhausen, 2007</td>
<td>Mycotic aortic pseudoaneurysm</td>
<td>Clinical picture of infection, positive blood culture, aortic imaging</td>
</tr>
<tr>
<td>Razavi, 2008</td>
<td>Mycotic aneurysm</td>
<td>*Unclear definition and diagnostic criteria</td>
</tr>
<tr>
<td>Clough, 2009</td>
<td>Mycotic aortic aneurysm</td>
<td>*All aneurysms of infective etiology</td>
</tr>
<tr>
<td>Sörelius, 2009</td>
<td>Mycotic aortic aneurysm</td>
<td>Clinical signs of infection, hematologic tests and culture, characteristic imaging. Positive culture not requisite.</td>
</tr>
<tr>
<td>Kan, 2010</td>
<td>Mycotic aortic aneurysm</td>
<td>Clinical course with infectious signs, positive blood or tissue culture and aortic imaging</td>
</tr>
<tr>
<td>Kan, 2011</td>
<td>Infected aortic aneurysm</td>
<td>Author switching terminology, but retaining diagnostic criteria: Clinical course with infectious signs, positive blood or tissue culture, and aortic imaging</td>
</tr>
<tr>
<td>Yu, 2011</td>
<td>Mycotic aortic aneurysm</td>
<td>Clinical signs of infection, characteristic imaging and intraoperative inflammation or purulence</td>
</tr>
<tr>
<td>Bisdas, 2011</td>
<td>Infected aneurysm</td>
<td>Supporting Wilson’s classification, and arguing for a change of terminology</td>
</tr>
<tr>
<td>Sedivy, 2012</td>
<td>Infected aortic aneurysm</td>
<td>Definition according to Wilson, diagnostic criteria unclear but excluding graft infections and fistulas, and positive culture is not a requisite</td>
</tr>
<tr>
<td>Uchida, 2012</td>
<td>Mycotic aortic aneurysm</td>
<td>Combination of clinical, imaging and pathological evidence</td>
</tr>
</tbody>
</table>

The diagnosis of MAA according to paper I-III consisting of a combination of clinical picture, laboratory findings and radiology is in itself appropriate, but may be confused with, or regarded as the same, as a secondary aortic infection. It is important to distinguish primary infections of the native aorta (e.g. an MAA) from secondary aortic infections, such as graft infections, secondary AEFs, and also inflammatory aneurysms and penetrating aortic ulcers because of their difference in course of natural history and management. Whether it should be named infected or mycotic aneurysm is misleading, and still – 130 years later – a matter casting shadows of confusion upon this disease, see table 3 in the Diagnosis chapter. Due to this unclearness in terminology and definition criteria, in addition to the rareness of MAA, MAAs and secondary aortic infections are sometimes mixed in the literature, making comparative analysis an even tougher task (Jones 2004, Teebken 2004, Lesèche 2001). If the subject of aortic infections should be taken seriously and regarded as science, and not as a matter of pure arbitrariness, these issues need to be addressed. Otherwise we will be stuck on the current level of knowledge and evidence regarding MAAs. In paper I-III an effort was made to be as explicit as possible with criteria for inclusion and exclusion.
**Figure 13.** The diagnosis of MAA is like a three-legged horse, unstable and unpleasant.

The dilemma and difficulties with proven positive culture for the diagnosis of MAA has been discussed in the *Bacteriology* and *Diagnosis* chapters.

“An obvious problem when studying a disorder of such low incidence, it must be emphasized that existing treatment options and strategies are based on clinical judgement and experience together with pathophysiological understanding of the disease process, and randomized trials comparing various therapeutic modalities are not likely.” - David Bergqvist, vascular surgeon, professor emeritus, Uppsala University

Owing to the rarity and variable nature of MAAs, a true comparison of open and endovascular treatment strategies is difficult, and the evidence for new treatment strategies will have to, mostly, rely on case series with adequate follow-up. It is, however, difficult, to compare results between different case series of MAA due to difference in case-mix, and low number of cases in each series. The same reasoning could be applied to the evaluation of the risk of secondary vascular infection after treatment with OA with VAWCM. However, paper III is an effort in comparing OR and EVAR.

The retrospective design of paper I and II is a limitation with risk of selection bias. However, during the study time-periods only a handful of patients with MAAs were treated with open repair at the contributing centres, which suggests this bias is minimal. This risk should be eliminated in paper III, since it is registry based, with prospectively registered data. A prospective study on treatment of MAA would be optimal but the feasibility may be questioned. It would require an international multicentre collaboration over a long time.

In paper IV, the median follow-up was 16 months, which may be too short, since graft infections typically occurs one to three years after both open and endovascular surgery (Tegler 2011).
Statistical limits

As a consequence of the rarity of the disease (MAA) and outcome (death, infection-related complication), all studies in this thesis suffer from small sample sizes, with risk of type II error. At the same time multiple testing (as in the regression analysis in paper II) results in risk of Type I error. There is always a trade-off between the risk of Type I and Type II errors, and usually a Type I error is considered a more serious problem. In some cases a Type I error is, however, preferable to a Type II error. With a very rare disease, such as MAA, it is a major undertaking to collect cases. Even though 16 major European centres were engaged, only 123 EVAR treated cases were collected in paper II, and 132 patients from 27 centres in Sweden in paper III. It is not likely to see a substantially larger study of this kind in the near future. It was therefore believed that it is of priority to explore the material as much as possible, albeit being aware of the risks of over-analysis of the data.

One could argue that a Bonferroni correction could have adjusted this, but this was not performed.

It is also likely that a Cox model underestimates the effect (death) of a postoperative infection complication, by failing to account of possible time free of infection in those who later suffer a postoperative infection. The timing (debut/ending) of postoperative infections (such as sepsis) is, however, difficult to define for which it is difficult to use a time-dependent covariate approach.

On results

Ideally, an MAA should be removed in its entirety, however paper I-III demonstrate that EVAR works as surgical solution for MAA. And paper III also shows superior results after EVAR compared to OR up to one year regarding survival. OR was even found to be the solely risk factor for all-cause death within three months in a multivariable regression analysis, with a hazard ratio of seven. Hence, the paradigm shift in treatment of MAAs in Sweden seems justified.

Regarding crude long-term survival of MAAs - 59% at 5-years and 39% at 10-years – the numbers are almost comparable to non-infected AAs. iAAA have a 5-year survival of 69%, and rAAA 42% (Mani 2009). In paper II the 5-year survival was 55% for endovascularly treated MAAs (both intact and ruptured) compared to 2732 patients in a US study with descending thoracic aortic aneurysm treated with TEVAR 1998-2007 with a 5-year survival of 62% for intact and 23% for ruptures (mean age 76 and 78 years). However, patients with aortic aneurysms due to infection differ in age and comorbidity compared to non-infected AAs.
The finding of postoperative ABx-treatment more than 6 months being a protective factor at 5-years in the multivariable regression analysis in paper III, paired with that 20% of patients have infection-related complications, indicate that these patients should be followed very closely with clinical follow-up including laboratory and radiological exams the first postoperative years. In paper II, a substantial part of patients who developed infection-related complications did so after termination of ABx, which were in most cases before the first six months. ABx should probably be administered for at least 6-12 months postoperatively, but maybe lifelong and especially in patients with a non-Salmonella positive culture result. Perhaps the continued ABx-treatment should be administered in mutual accordance with specialists in infectious diseases for best possible results. The finding that suprarenal aneurysm location and rupture are risk factors associated with death at 5-years may indicate that these patients should be re-evaluated even more vigilantly. However, these results support parts of earlier findings in smaller studies (Oderich 2001, Hsu 2004, Kan 2007, Yu 2011).

In publications with the best surgical results and least rates of recurrent infections, all study groups (both OR and EVAR) have used an approach where ABx is administered until infection is controlled, sometimes up to four to six weeks prior to surgical intervention (Hsu 2002, Kan 2012, Uchida 2012). These results thus suggests that if feasible, a period of intravenously administered ABx before surgery, to eradicate as much bacteria as possible from the aneurysm and the bloodstream, and also to revoke sepsis induced organ failure, could have a beneficial effect on long-term outcome. However, such strategy might be very risky because of the high risk of rupture.

In complex cases like these of MAA, one single therapeutic solution cannot be the solution to all cases. Therefor it is important to develop therapeutic strategies in order to achieve best clinical outcome. The possibility to offer a minimal-invasive surgical intervention like EVAR in old, debile patients with an anatomically challenging MAA is of great importance, a reasoning in conformity of what has been found with uninfected rAAA (Karthikesalingam 2014).

Thoracic MAAs have a higher mortality compared to abdominal with OR (Moneta 1998, Oderich 2001, Yu 2011), and mixing results with abdominal and thoracic aneurysms treated with EVAR might lead to an overestimation of the benefits of EVAR to OR in abdominal MAAs and hence an underestimation of its superiority in thoracic MAAs. Paper III reduced heterogeneity by only analysing abdominal MAAs, and still demonstrating better results up to one year for EVAR when compared to OR, without increasing the risk of recurrence of infection or reoperation.

On paper IV. The two patients with graft infections after EVAR for AA and treatment with OA and VAWCM, both suffered from colonic ischemia requiring resection, and it is likely the subsequent graft infections were a result of hematogenic seeding rather than contamination from the OA, and
through the aortic wall, when the retroperitoneal space was intact. Nevertheless, the poor prognosis among patients needing prolonged OA after AA-surgery emphasizes the importance of early closure, if possible. To determine the risk of subsequent vascular infection after AA surgery and OA treatment, a study with a larger cohort of patients with longer follow-up would be ideal.

Table 7. Publications evaluating OA after AA repair.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design</th>
<th>No of patients</th>
<th>TAC method</th>
<th>No of graft infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker, 2007</td>
<td>Retrospective</td>
<td>13</td>
<td>Vacuum pack</td>
<td>Not studied</td>
</tr>
<tr>
<td>Pettersson, 2007</td>
<td>Retrospective</td>
<td>4</td>
<td>VACM</td>
<td>0</td>
</tr>
<tr>
<td>Ross, 2009</td>
<td>Retrospective</td>
<td>20</td>
<td>Vacuum pack plus mesh bridge</td>
<td>0</td>
</tr>
<tr>
<td>Mayer, 2009</td>
<td>Retrospective</td>
<td>20</td>
<td>Bogota bag</td>
<td>Not studied</td>
</tr>
<tr>
<td>Kimball, 2009</td>
<td>Retrospective</td>
<td>21</td>
<td>Vacuum pack</td>
<td>1</td>
</tr>
<tr>
<td>Seternes, 2010</td>
<td>Prospective</td>
<td>9</td>
<td>VACM</td>
<td>0</td>
</tr>
<tr>
<td>Sörelius, 2013</td>
<td>Prospective</td>
<td>30</td>
<td>VAWCM</td>
<td>2</td>
</tr>
</tbody>
</table>

A historical pitfall in interpreting outcome – a word of caution

The comparisons of outcomes between modern EVAR for MAA with older series using standard surgical approaches must be tempered by the progress in antibiotic therapy and intensive care management. On the other hand one must take in account the evolution endovascular technology has gone through during the 14-year study period in paper II. The minimal-invasive approach may also result in a different case-mix for EVAR vs OR. However, year of surgery was not a significant predictor in outcome in the multivariable regression analysis in paper III.
Strengths of thesis

Although being small, as already mentioned, paper I-III were at the time of their respective publication the largest studies on EVAR for MAA and on MAA in general (although paper III at the time of writing is only a manuscript). Paper II is unique in the fact that it is a multinational, multicentre collaboration, which is an important step forward in improving research of this rare disease.

Paper III is a population based cohort, which is the first study ever which allows a comparison between OR and EVAR without collecting cases from the literature (Kan 2010).

Paper IV is, so far, the largest, study attempting to assess the risk of vascular infection after prolonged OA.
Future research on aortic infections

To avoid leaving treatment of aortic infections into a grey zone based upon experience, judgement and small case series, subject 1 in the Discussion needs to be addressed. A clear and uniform definition of these diseases would work as a platform for future research in the field:

An international consensus document settling definition, terminology and criteria for the diagnosis of MAA, and also aortic graft infection and aorto-enteric fistulae is vindicated. To define one and not the other is just a half-measure. This would facilitate research, enabling standardization of clinical and imaging follow-up, make comparative analysis easier and thereby elevate the level of knowledge of MAA. In turn, this would make treatment guidelines possible regarding OR, EVAR and choice of ABx including the crucial question of duration.

This, in addition to an international vascular registry of rare vascular diseases would enable larger cohorts, and could on a long-term view lead to a registry based randomized controlled trial on EVAR versus OR for MAA in different anatomic locations.

To comprehend if bacteria which cause MAA have unique properties or not, and how they infect the vascular endothelium, isolates should be collected prospectively and analyzed regarding serotype and genome sequencing to identify possible specific characteristics.

To use antibiotics as efficiently and appropriately as possible further research has to be done, preferably in unison between vascular surgeons and specialists in infectious diseases.

The subgroup of HIV-related infected aortic aneurysms is challenging, and needs further pathophysiologic research, for making correct diagnosis, detecting patients at risk and develop strategies in management.

A proposition for future definition, terminology and diagnostic criteria for MAA could be:
Definition and terminology

An infected native aortic aneurysm, INAA, is defined as a protuberance caused by an infection with certain morphologic characteristics in the native aortic wall, irrespective of size. The aneurysm grows rapidly and without expedient treatment ruptures with fatal outcome. The infective agent is dominantly bacteria, but extremely rare cases of fungi have been reported. The common definition of aortic aneurysm is not applicable to INAA because their morphology is predominantly saccular, multilobular or somewhat eccentric but could also be fusiform, and not based on its aortic diameter, hence the term protuberance is chosen in this definition.

INAAs can arise due to septic emboli lodging in the vasa vasorum of the aorta from infective endocarditis, blood-borne bacteria inoculated in the aortic wall during septicaemia, infection spreading from adjacent organ e.g. osteomyelitis and psoas abscess, and HIV-related infected aortic aneurysms.

Infection of pre-existing aneurysm due to blood-borne bacteria is a particular entity, which should be treated as INAA.

Aortic aneurysms due to infection that develop in a patient who has previously undergone aortic surgery and are located adjacent to the old graft are probably secondary to a graft/stentgraft infection, and should be called graft infection related aortic aneurysm, GIAA.

Recurrent infected aortic aneurysm, RIAA, is an aneurysm that develops in an aorta, which has previously been treated for INAA, at a distant location to the graft/stentgraft.

The distinction between an INAA and graft infections and aorto-enteric fistulas is crucial because of their difference in pathophysiology, course of natural history and management.

Diagnosis

Since there is no pathognomonic symptom, laboratory or radiological sign the diagnosis of INAA is syndromic. The diagnosis of INAA is based on a combination of the following three criteria and exclusion of differential diagnosis stated below:

- **Clinical presentation** (pain, fever ≥38, sepsis, concurrent infections etc)
- **Results of hematologic tests** (elevated inflammatory markers and cultures)
- **Radiologic findings on CT/MR** (e.g. saccular multilobular aneurysms or eccentric aneurysms with narrow neck, rapid expansion, periaortic gas formation within the aneurysm thrombus, periaortic soft tissue mass)
A plausible algorithm for making the diagnosis could be:

- **Definitely INAA:** 3/3 diagnostic criteria and no differential diagnosis listed below being more likely.
- **Probably INAA:** 2/3 diagnostic criteria and no differential diagnosis listed below being more likely.
- **Not likely INAA:** 1/3 diagnostic criteria or differential diagnosis listed below being more likely.

**Differential diagnosis:**

This could work as a provisional platform and something researchers could relate to. Then of course this definition, terminology and diagnostic criteria have to be accepted, eventually implemented into practice and revised again and again.
Summary of thesis in Swedish

Populärvetenskaplig sammanfattning

Kunskapsläget om behandling av mykotiska (infekterade) aortaaneurysm och graftinfektioner efter aortakirurgi med öppen buk-behandling är ytterst bristfälligt, främst beroende på att tillstånden är mycket ovanliga. Samtidigt är de båda ytterst allvarliga tillstånd med utmanande och resurskrävande handläggning, samt hög dödlighet. Traditionellt behandlas MAA med extensiv öppen kirurgi med revaskularisering i form av in-situ eller extraanatomisk bypass, dock med hög morbiditet och mortalitet. Bevisläget för denna strategi är mycket bristfällig.

Denna avhandling syftar till att utvärdera resultat av minimal-invasiv, skendovaskulär behandling (EVAR) av mykotiska aortaaneurysm (MAA), jämföra dess resultat med traditionell öppen kirurgi avseende överlevnad och risk för återkommande infektion, samt att utvärdera risk för graftinfektion efter behandling med öppen buk efter aortakirurgi.

Delarbete I. En retrospektiv, singel-centerstudie av 11 patienter med MAA behandlade med EVAR. Studien visade goda resultat på kort sikt, med en överlevnad på 91 % vid 30 dagar, och en acceptabel överlevnad på 76 % vid 1 år. Postoperativt dog en patient av sepsis och en av blödande aortoenterisk fistel. Två drabbades av sepsis men överlevde.

Delarbete II. En retrospektiv internationell multicenterstudie av 123 patienter som behandlats med EVAR för MAA. Studien bekräftade resultaten i delarbete I, och kunde dessutom visa att EVAR också är ett hållbart behandlingsalternativ på lång sikt, med en 5-årsöverlevnad på 55 % och vid 10 år 41 %. Totalt 19 % dog av en infektionsrelaterade komplikationer, främst under det första postoperativa året. Icke-Salmonella-positiv blododling fanns vara en prediktor för sen infektionsrelaterad död.

Delarbete III. En retrospektiv nationell studie av alla patienter i Sverige som behandlats för abdominella MAA (MAAA) mellan 1994 och 2014. Studien inkluderade 132 patienter, ungefär hälften vardera opererade med öppen kirurgi och EVAR. Den totala överlevnaden var 86 % vid 30 dagar, 79 % vid 1 år och 59 % vid 5 år. EVAR utgjorde 60 % av ingreppen. Överlevnaden

**Delarbete IV.** En prospektiv multicenterstudie av 30 patienter som behandlats med öppen buk efter aortakirurgi. Infektiösa komplikationer såsom graftinfektioner var ovanliga men sågs i två fall med tarmischemi som krävde tarmresektion och långvarig öppen buk-behandling, varav en dog.
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Last but not least, my friends.

“You don’t climb trees? You’re missing out”
– Michael Jackson


Crane, A (1937). "Primary multilocular mycotic aneurysm of the aorta". Arch Pathol 24:634.


Ponfick (1873). "Ueben embolische aneurysmen, nebst bemerkungen uber das acute herzaneurysma (herzge schwur)." Virchows Arch. 58:528.


Appendix
Multicenter study of endovascular repair of MAA

Definition of MAA (mycotic aortic aneurysm):

A MAA is defined as a primary infected aortic aneurysm of any part of the aorta

The diagnosis of MAA is based on one or several of the following criteria:
- Clinical presentation (sepsis, concurrent infections etc)
- Results of hematologic tests (elevated inflammatory markers and cultures)
- Radiologic findings on CT/MR (e.g. saccular multilobular aneurysms or eccentric aneurysms with narrow neck, rapid expansion, periaortic gas formation within the aneurysm thrombus, periaortic soft tissue mass)

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Case specific comments (if not covered in the protocol) .................................................................................................................................
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1) Preoperative data:

Age (at repair): ________________________ years  Sex: woman ☐ man ☐

Medical history:

Cardiovascular disease:
- Hypertension ☐, Stroke/TIA ☐, MI/angina ☐, COPD ☐
- Other (specify) __________________________________________________________

Immunosuppressive disease or medication:
- Renal failure ☐, Diabetes ☐, HIV ☐, Steroids ☐
- Other (specify) __________________________________________________________

Concomitant infection:
- Osteomyelitis ☐, Urinary tract ☐, Tuberculosis ☐, Gastroenteritis ☐, Soft tissue ☐
- Other (specify) __________________________________________________________

Clinical presentation / lab:
- Pain ☐, Fever ☐, Chock (SBP<90) ☐
- C-reactive protein Specify level _________________________________________________
- Leucocytes Specify level ______________________________________________________
- Blood culture: Neg ☐ / Pos ☐ specify ____________________________________________
- Other culture: Neg ☐ / Pos ☐ specify ____________________________________________

Aneurysm data:
- Classification: Intact ☐, intact/symptomatic ☐, contained rupture ☐, rupture ☐

Location (multiple answers possible):
- Ascending ☐, Arch ☐ (including: BCT ☐, LCA ☐, LSA ☐)
- Descending ☐, Suprarenal ☐ (including: CT ☐, SMA ☐,RA ☐)
- Infrarenal ☐, Common iliac ☐ (including: HA ☐)

CT-finding (multiple answers possible):
- Rapid expansion ☐, Saccular ☐, Multilobular ☐, Peri-aortic gas ☐
- Periaortic soft tissue mass ☐
2) Treatment data

Surgery data:

Date of EVAR (yy/mm/dd): .................................................................

Type of aortic repair:

EVAR ☐, TEVAR ☐, bEVAR ☐, fEVAR ☐
Other (e.g. chimneys, debranching) ..................................................

Device:

Gore ☐, Cook ☐, Medtronic ☐, Other ☐ (specify) .........................................
Number of device(s) / Cover length: ........................................... / ........................................

Adjunctive procedures

Amputation ☐ (specify) .............................................................................
Drainage of abscess ☐ (specify) ..............................................................
Other (specify) ......................................................................................

Antibiotic treatment:

<table>
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<th>Type (generic name)</th>
<th>length (weeks)</th>
<th>Lifelong</th>
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</thead>
<tbody>
<tr>
<td>1)</td>
<td></td>
<td>No ☐ Yes ☐</td>
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<td>7)</td>
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</tr>
<tr>
<td>8)</td>
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<td>No ☐ Yes ☐</td>
</tr>
</tbody>
</table>
3) Postoperative / follow-up data

Total follow-up time (months) .................................................................

Death at end of follow-up: No □, Yes □
If Yes, time after repair (days or months) ....................................................
If Yes, cause of death ................................................................................

Postoperative imaging: No □, Yes □
If Yes, specify (type, timing, and outcome): ..................................................
..............................................................................................................

Bridge to open surgery: No □, yes □
If Yes, specify (reason, type, timing, and outcome): .....................................
..............................................................................................................

Complications:
No complications: □

Infectious complication:
  Recurrent/persistent sepsis □, graft infection □, recurrence of aneurysm □
  If Yes, specify (type, timing, treatment, and outcome): ............................
  ...........................................................................................................

EVAR-related complications:
  Endoleak □, Migration □, Occlusion □
  If Yes, specify (type, timing, treatment, and outcome): ............................
  ...........................................................................................................

Other complications: (eg MI, renal failure)
  Major bleeding □, MI □, Renal failure □, Stroke □, Paraplegia □
  If Yes, specify (type, timing, treatment, and outcome): ............................
  ...........................................................................................................
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