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Current Topics of Infectious Infected Aneyrysm

Infected Aneurysm: Current Management

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Despite of progression of medical and surgical treatment for patients with vascular disease, infected aneurysm still remains as a challenging vascular disease to treat in current practice.

In 1885, Osler coined "mycotic aneurysm" to provide the first description of infected aneurysm caused by bacterial endocarditis.[1)]

At that time, the term "mycotic" was applied to any infection by bacterial or fungal infection.

Infected aneurysm is a more comprehensive term, which encompasses primary infection of native artery resulting in aneurysm and infection of preexisting aneurysm. Although infected aneurysms are rare in its frequency, they nevertheless represent a life-threatening disease with high incidence of arterial rupture and recurrence even after treatment.

Etiology of Infected Aneurysm

Normal arterial wall is resistant to the bacterial invasion even in bacteremia status. But bacterial invasion into the arterial wall through hematogenous route is prone in immune-compromised patients such as diabetes mellitus, acquired immune deficiency syndrome, malnutrition, liver cirrhosis or in patients with arterial luminal defect (atherosclerotic plaque or ulceration, preexisting aneurysm or arterial coarctation).

There have been changes in the underlying causes and infecting organisms of the infected aneurysm. **Table 1** shows underlying etiology and common infective organisms of infected aneurysm. The relative frequency of mycotic aneurysm caused by bacterial endocarditis decreased to less than 10% in accordance with decreased incidence of bacterial endocarditis while arterial psuedoaneurysm related with arterial trauma increased.

Contiguous aortitis is defined as an aortic wall infection due to adjacent infective focus such as osteomyelitis of vertebral body, pancreatitis, retroperitoneal or psoas abscess or lung, gastrointestinal or urinary tract infection. Native arterial wall infections often lead to aneurysm formation and results in aneurysm rupture while some patients develop non-aneurysmal suppurative arteritis.

Infected arterial aneurysms caused by trauma are almost always pseudoaneurysms whether it is iatrogenic or not. Recently increasing uses of arterial puncture or catheterization provide one of major causes of infected pseudoaneurysm. In a drug abuser, intraarterial injection using contaminated needle is another cause of infected aneurysm in certain parts of the world.

Microbiology

Before the advent of antibiotics, the most common underlying cause of infected aneurysm was bacterial endocarditis, which predominantly occurred in the ascending aorta and aortic arch. At that time, common bacterial organisms are nonhemolytic streptococci, staphylococci and pneumococci. After advent and widespread use of antibiotics, salmonella species became the most common infective organism of infected aneurysms, which often developed at abdominal aorta.[3, 4)]

Salmonella is the most prevalent organism associated with microbial aortitis in non-aneurysmal aorta. Particularly areas of intimal disruption such as with atherosclerotic plaque or ulceration are preferred sites for bacterial invasion. Clinically aortic bifurcation or aortic segment with atherosclerotic plaque, ulceration is prone to Salmonella infection.[4–7)]

Before 1965, *Salmonella* was the most common organ-

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Table 1 Etiology and common organisms of arterial infection

	Mycotic aneurysm	Microbial arteritis	Infection of existing aneurysm	Post-trauamtic existing aneurysm
Etiology	Bacterial endocarditis	Bacteremia	Bacteremia	Trauma Drug addiction
Age (year)	30–50 years	> 50 years	> 50 years	< 30 years
Incidence	Rare	Common	Unusual	Became more frequent
Location	Aorta Visceral Intracranial Peripheral	Aortoiliac segment with atherosclerotic plaque	Infrarenal aorta	Femoral, carotid
Bacteriology	Gram (+) cocci	Salmonella, others	Staphylococcus, others	Staphylococcus aureus, polymicrobial
Mortality	25%	75%	90%	5%

(From Wilson SE et al.)[2]

ism of infected arterial aneurysm followed by *staphylococcus aureus.* Since then, *Salmonella* decreased, while *Staphylococcus aureus* rose to 30%. In accordance with this change, the frequency of endocarditis as the underlying etiology has decreased to 10% while trauma increased from 10% to 54%.[8]

The most common location of trauma-related infected aneurysm is femoral artery. These changes in bacterial species and the location of infected aneurysms are the results of the increased frequency of arterial puncture or catheterizations.

In pathogenesis of infected aneurysm, microorganisms are different between organisms infecting preexisting aneurysm and organisms causing infected aneurysm in non-aneurysmal artery. Common organisms of infection of preexisting aneurysm are Gram positive organisms such as staphylococcus or streptococcus. Of those staphylococcus aureus is the most prevalent.

In aortitis of non-aneurysmal aorta, Salmonella species are the most prevalent organisms. In those patients with Salmonella aortitis, arterial luminal irregularity is an important risk factor for the arterial wall invasion by microbial organism. In pathogenesis of aneurismal formation in bacterial infection of the arterial wall, production of proteinase such as collagenese, elastase, neutrophil elastases or metalloproteinases are known to be associated with aneurysm formation.

Gram negative organism can cause more virulent arterial infection than in Gram positive infection and makes the aneurysm more prone to rupture and associated with higher mortality.

There are some differences in infecting organisms geographically. Reports from Europe or North America described Gram positive staphylococcus was more prevalent while reports from east Asia described Gram negative Salmonella species were more prevalent as infecting organism.[9, 10]

Clinical Features

The clinical manifestations of infected aneurysm can be determined by the location, infecting organism, and whether it is caused by primary arteritis or an infection of pre-existing aneurysm.

Prominent clinical features of infected aneurysm of the peripheral artery are local pain, tenderness, heatness, hyperemia at overlying skin and pulsatile bulging over the artery. As described above, common femoral artery is the most common site of infected aneurysm currently.

Contrast to infected aneurysm occurring in peripheral artery, infected aortic aneurysm presents with vague clinical symptom. The characteristic clinical features of infected aortic aneurysm are tender pulsating abdominal mass, fever, leukocytosis and positive blood culture. Pain is usually present in the abdomen but may occur as back or flank pain and is usually vague in nature. Therefore, it provides nonspecific diagnostic clue.

Associated history of immune-compromized conditions such as diabetes mellitus, long-term use of steroid, chemotherapy, immunosuppression, chronic renal failure or malnutrition can be diagnostic clues of infected aneurysm. Coexisting spinal osteomyelitis or retroperitoneal abscess can also be a source of a contiguous infection to the aorta.



Fig. 1 Infected aortic aneurysm due to Salmonella infection, which was treated by transaortic patch closure of aneurismal neck using autogenous hypogastric artery patch and antibiotic therapy: (left top) preoperative CT angiogram, sagittal view; (right top) preoperative CT angiogram, coronal view; (left bottom), postoperative CT angiogram, sagittal view; (right bottom) postoperative, CT angiogram.

Salmonella aortitis may appear after a febrile gastroenteritis. The common location of primary aortitis and aneurysm formation is at the posterior wall of the suprarenal or supraceliac aorta (**Fig. 1**). Contrary to the primary microbial aortitis, the most common location of secondary infection of pre-existing aneurysm is infrarenal aorta presumably due to the most common location of abdominal aortic aneurysm (AAA) in that segment of aorta.

According to the virulence of the infecting organism, some patients seek medical service with prolonged history of systemic symptoms such as low-grade fever, weight loss, anorexia or weakness while others presents with typical local symptom, aneurysm rupture or sepsis.

Aorto-eteric or aorto-bronchial fistulae are one of disastrous clinical features in patients with infected aortic aneurysm. As a remote symptom of infected aortic aneurysm, we encountered one patient complaining of eye pain and swelling which rapidly progressed into septic endophthalmitis requiring enucleation.

Diagnosis

Almost all untreated infected aneurysms eventually lead to rupture. Therefore, when an infected aneurysm is suspected, urgent confirmatory diagnosis and definitive treatment are essential. Basically, a high index of suspicion is essential for the diagnosis of infected aneurysm particularly when the patient has had a recent febrile illness, prior history of arterial trauma or catheterization, bacterial endocarditis or other immune compromising conditions.

Leukocytosis and erythrocyte sedimentation rate (ESR) are sensitive but not specific in diagnosis of in-

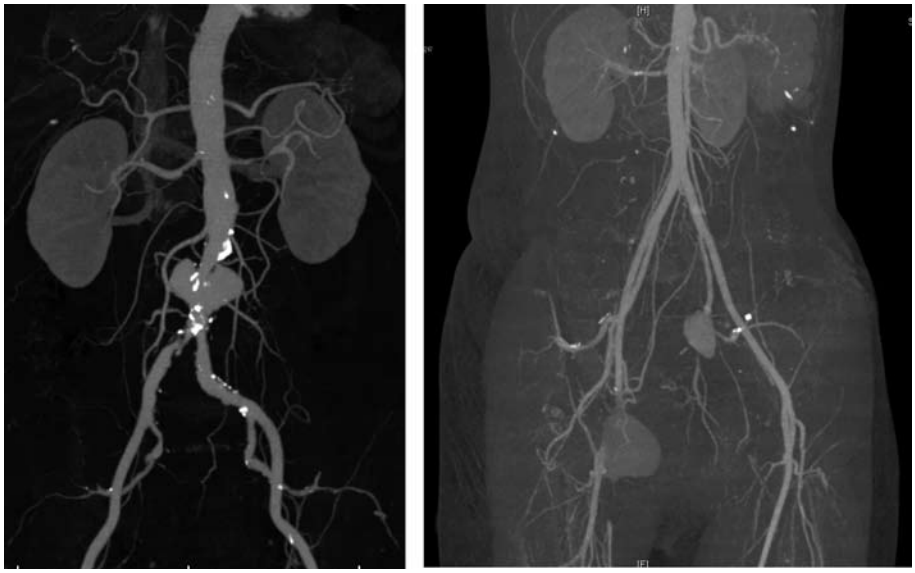


Fig. 2 CT angiogram in patients with infected aortic aneurysms: left) lobulated and irregular shaped aortic aneurysm; right) multiple aneurysms involving right femoral and left hypogastric artery in a patient with prior history of bacterial endocarditis.

fected aneurysm. Patients with an arterial aneurysm with positive blood cultures should be considered to have an infected aneurysm until proven otherwise. Conversely, negative blood cultures are not sufficient to exclude infected aneurysm because positive cultures can be obtained in only 50–70% of patients with infected aneurysm.[3,7)]

Contrast-enhanced computed tomography (CT) is initial diagnostic test of choice in patients with infected aneurysm. CT findings suggestive of infected aortic aneurysm are saccular or multilocular appearance of aneurysmal sac with adjacent normal vessel (**Fig. 2**) or periaortic infection focus such as psoas abscess or osteomyelitis of adjacent vertebral body (**Fig. 3**). Periaortic air shadow (**Fig. 4**), rapid change of aneurysmal contour or size, local contained rupture or false aneurysm formation is also suggestive of infected aneurysm.

Although radioisotope-tagged leukocytes (**Fig. 5**) scans can be used in the diagnosis of infected aortic aneurysm, it has not always been accurate in confirming in diagnosis of infected aneurysm.[11)]

Magnetic resonance imaging (MRI) can be used for the diagnosis of deep-seated infected aneurysm or when contrast-enhanced CT scan is contraindicated.[12)]

Recently, positron-emission tomography (PET)-CT scan (**Fig. 6**) was applied in the diagnosis of infected aortic aneurysm. Reeps C. et al.[13)] reported finding of increased aortic FDG uptake on 18F-fluorodeoxyglucose (FDG) positron-emission tomography (PET)-CT scan was correlated with inflammation, histopathologic characteristics of aneurysm wall instability, and clinical symptoms.



Fig. 3 Abdominal CT scan shows periaortic fluid collection and vertebral body erosion.

TREATMENT

Before surgical treatment, echocardiography, contrast-enhanced thoracoabdominal CT (or MRI), blood test,

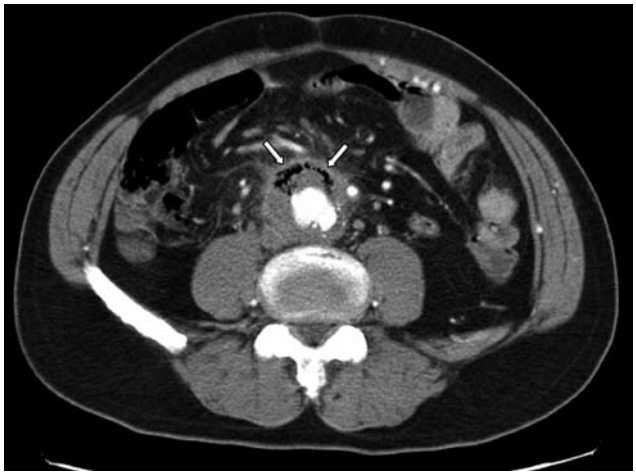


Fig. 4 Abdominal CT scan shows preiaortic gas shadow (arrow) in a patient with an infected aortic aneurysm resulting in aorto-duodenal fistula.



Fig. 5 Tc 99m leukocyte scintigram shows uptake of leukocytes (arrow) around abdominal aorta in a patient with infected abdominal arotic aneurysm.

Gram stain and blood culture and sensitivity test are essential steps for patients with infected aneurysm. Two essential components in treatment of infected aneurysm are surgical removal of infected tissue including arterial wall and culture-specific antibiotic therapy.

1) Surgical treatment

If an infected aneurysm is diagnosed, surgical removal of infected aneurysm is almost always required. The timing of surgical intervention can be determined by estimated risk of aneurysm rupture and surgical risk based on the patient's general condition.

But we have to keep in mind is that infected aortic aneurysms are prone to rupture regardless of the size of the aneurysm.[14] Therefore undue delay of surgical intervention should be avoided. Emergency operation is recommended in patients who has a ruptured aneurysm or is septic and unstable. Otherwise surgery can be performed on an early elective basis under the coverage of antibiotics.

General principles of surgical treatment include obtain tissue specimen for gram stain and tissue culture, wide debridement of all infected tissues including infected arterial wall, copious irrigation of surgical field with antiseptic solution, arterial reconstruction and prolonged postoperative use of specific antibiotics.[15] After removal of infected abdominal aorta, there are several options to reconstruct the aorta. The classic approach is removal of whole infected aorta and creation of axillo-bifemoral bypass through the uninfected plane. In choosing an order of procedures between excision of infected aortic aneu-

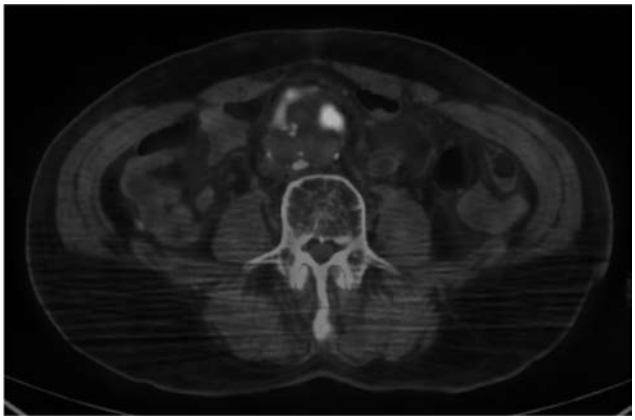


Fig. 6 18F-fluorodeoxyglucose(FDG) positron-emission tomography (PET)-CT scan shows aortic FDG uptake in a patient with infected aortic aneurysm.

rysm and axillo-bifemoral bypass, it depends on risk of aortic rupture and an urgency of lower extremity arterial reperfusion.[16, 17] The advantage of this procedure is to avoid use of new prosthetic graft in an infected field. But it has disadvantages of risk of blowing out of aortic stump and inferior graft patency compared to in situ aortic reconstruction. And this procedure also has potential risk of infection of the axillobifemoral bypass grafts.[18] Though Yeager et al.[19] reported an acceptable operative risk and long-term limb salvage rates, overall perioperative mortality rate was 20% after treatment of infrarenal aortic infection.

Recently some authors reported "in-situ" aortic reconstruction after removal of infected aortic aneurysm. The proposed merits of in-situ aortic reconstruction are better patency, superior hemodynamic property compared to axillo-bifemoral bypass where as it carries higher risk of graft infection by putting the new aortic graft in the infected surgical field.

To reduce the risk of aortic graft infection, various graft materials and adjuvant procedures have been introduced including antibiotic releasing beads implantation in the perigraft tissue, graft wrapping with omentum, use of rifampin-bonded graft, silver coated Dacron graft, autogenous femoro-popliteal vein graft or cryopreserved allograft. Chan et al.[20] reported a 14% mortality rate and 5% reinfection rate after in situ aortic reconstruction using rifampin-bonded Dacron graft.

Bandyk et al.[21] reported results of in situ replacement for patients with prosthetic graft infection based on a treatment algorithm consisted of graft excision with or without ex situ bypass grafts for patients presenting with sepsis or graft-enteric erosion, whereas in situ replacement with autogenous vein, rifampin-bonded polyester, or polytetrafluoroethylene [PTFE]) graft in patients with less virulent gram-positive graft infection, in particular infections caused by Staphylococcus epidermidis. They concluded that In situ replacement was a safe and durable option in patients without sepsis, anastomotic dehiscence, graft enteric fistula, or aortic infection by virulent, antibiotic–resistant bacterial stains. In other words, in situ replacement with prosthetic graft is recommended primarily for patients with Gram-positive bacterial infections, free of frank purulence or in areas not amenable to conventional management.

For in situ aortic reconstruction, allograft is another option to reduce reinfection rate and to improve survival.[22] Arterial allografts were usually harvested from multi organ donors and prepared with antibiotics and cryopreserved at tissue bank.[23] On experimental studies, cryopreserved arterial allografts show to have better resistance to infection by allowing transfer of antibiotics and immunocompetent cells through the allograft wall and into the perigraft space after implantation.[24–26] In 2002, early results of the United States cryopreserved aortic allograft registry for patients with infected abdominal aorta were reported.[27] According to the multicenter registry report, indications for implantation of cryopreserved aortic allograft were aortic graft infection (77%), mycotic aortic aneurysm (14%) and aorto-enteric fistula (7%). The 30-day surgical mortality rate was 13% and overall mortality was 25% during the follow-up period (mean, 5.3 months; range, 1–22 months) including 4% of graft-related mortality. They concluded that in situ aortic reconstruction with cryo-preserved aortic allograft in infected fields carries a high mortality rate, but most deaths did not result due to allograft failure. However, they warned against graft reinfection and lethal hemorrhage after implantation of cryopreserved aortic allograft. Another multicenter study demonstrated a high mortality rate (21%), and a high amputation rate (14%) with the use of cryopreserved aortic allografts but fewer graft-related complications.[28] A French group reported a long-term (mean 35.4 months, range 6–101 months) results of cryopreserved allograft implantations for 28 consecutive patients with in infected prosthetic grafts and mycotic aneurysms of the abdominal aorta. According to them, an overall treatment-related mortality rate was 17.8% (17% for graft infection, 20% for primary aortic infection). The overall 3-year survival was 67%. There was no early or late amputation. There were no persistent or recurrent infection, and none of the patients received long-term (> 3 months) antibiotic therapy.[29] E. Kieffer et al.[30] reported the world-largest, single center series of allograft replacement for infrarenal aortic graft infection. After using both fresh (n = 111) and cryopreserved allografts (n = 68) for infrarenal aortic graft infection, they observed that early and long-term results of allograft replacement were at least similar to those of other methods to manage infrarenal aortic graft infections. These complications such as graft rupture or aneurysmal dilatation were significantly reduced by using cryopreserved allografts rather than fresh allografts and by not using allografts obtained from the descending thoracic aorta.

Recently a single center experience of arterial reconstructions with cryopreserved human allografts in the setting of arterial infection was reported.[31] According to the study, after 57 arterial reconstructions using cryopre-

served human allografts (18 abdominal aorta, 39 iliofemoral/femoro-popliteal or prosthetic infections), they reported superior 1-year procedure related mortality after use of cryopreserved human allografts over other patients group used prosthetic graft (7.0% vs 13.2%). They concluded that cryopreserved human allograft arterial reconstruction was a viable alternative to traditional methods of vascular reconstruction in patients without available autogenous conduit and when expedient reconstruction is required. In midterm follow-up, cryopreserved allografts appear to be resistant to subsequent reinfection, thrombosis, or aneurysmal dilatation. Several disadvantages of cryopreserved allograft were also reported including late development of aneurysmal dilation, graft rupture and calcification caused by allograft degeneration.

To avoid graft infection after In situ implantation of aortic graft, aorto-iliac reconstruction with autogenous femoro-popliteal vein graft can be used. This technique has been reported to have a lower mortality, amputation rate and longer primary patency compared to extraanatomic bypass. Compared to other in-situ aortic reconstruction procedures using prosthetic or cryopreserved allograft, it needs longer operation time and can give greater surgical insult to the patients due to additional skin incisions for harvesting femoro-popliteal veins. Even though the frequency is low, this procedure can be followed by complications, such as compartment syndrome (12%) of lower leg, deep venous thrombosis (15%) or even pulmonary embolism (2.4%).[32]

Endovascular stent graft placement is introduced as another option to treat infected aneurysm. Recently, several case reports have been published describing various results of endovascular aortic stent grafting for patients with infected aortic aneurysm. Theoretically, endovascular aortic stent grafting has significant advantages over open aneurysm repair of infected aneurysm as it can avoid a large skin incision and pain, systemic heparinization, aortic cross-clamping, and blood transfusion. However, putting an endovascular stent graft in an infected environment is against surgical principles. Kan CD et al.[33] conducted a literature review of outcomes after endovascular stent graft treatment for mycotic aortic aneurysm using MEDLINE searching. According to them 30-day survival rate was 89.6% and 2 year survival was 82.2%. They concluded that endovascular aortic stent grafting for patients with infected aortic aneurysm seems a possible alternative method. But persistent infection is closely associated with a poor prognosis after EVAR treatment. When patients present with rupture or have fever, the EVAR method should be considered as a temporary measure to achieve hemodynamic stability. If the fever persists after the EVAR, a definite open surgical treatment is recommended.

At present, long-term results of EVAR for infected aneurysm were not reported but the short and midterm outcomes of this treatment modality have been promising when compared with conventional surgical techniques.[34, 35] To avoid infection of the aortic stent graft, early systemic use of broad-spectrum antibiotics followed by long-term use of appropriate antibiotics determined by culture and sensitivity tests; use of antibiotic-coated endoprosthesis; adjunctive procedures such as surgical debridement or percutaneus drainage are also recommended.

2) Antibiotic therapy:

Antibiotic therapy is an essential part of management but they are ineffective unless infected aneurysm is removed.[36] Once the diagnosis of infected aneurysm is made, broad spectrum antibiotics should be started until the results of the blood or tissue culture have been obtained. For patients with infected aortic aneurysm with no known proven organism, antibiotics to combat Salmonella species such as chloramphenicol, ampicillin, quinolone or a third generation cephalosporin should be included.

Regarding to the duration of antibiotic therapy, there are no definitive recommendations, but minimum of 6 weeks has been widely accepted. In certain cases, long-term oral antibiotics may be followed after intravenous therapy.

The prognosis of the native arterial infection depends on type of presentation (presence of rupture, sepsis), virulence of infecting organism, and patient's general condition (comorbidity, immune status etc). Reported mortality rates of infected abdominal aortic aneurysm was 23% to 31%. Reportedly, higher mortality was reported after treatment of infected aortic aneurysm associated with rupture, suprarenal involvement, and Gram negative organism infection.

For the treatment of infected aortic aneurysm, I personally perform in situ aortic reconstruction with cryopreserved human allograft and omental coverage after removal of infected aneurysm. For patients with a small saccular aneurysm at suprarenal or juxtareanal aorta, I performed autogenous arterial patch closure of the aneuyrsmal neck through the vertical aortotomy between 2 renal arteries. We used autogenous hypogastric artery to make a patch for those patients.[37]

For patients with aorto-duodenal fistula, axillo-bifemoral bypass or in situ aortic reconstructions with cryopreserved allograft is used in patients showing gross purulence whereas in situ aortic reconstruction with PTFE graft and omentum coverage in patients showing no gross purulence. We recommend omental coverage of graft for all patients who are undergoing in situ aortic reconstruction due to infected aortic aneurysm. To make omental tissue long enough to cover whole aortic graft, colonic attachment of great omentum is freed from the transverse colon and it is taken down to the distal aorta through a new opening at the transverse mesocolon.

Our strategy of antibiotic therapy is 4 weeks of intravenous antibiotic therapy followed by 2 months of oral antibiotics.

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