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SYSTEMATIC REVIEW

Systematic Review of the Management of Mycotic Aortic Aneurysms

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WHAT THIS PAPER ADDS

This paper is the first systematic literature review on the rare and therapeutically demanding disease of mycotic aortic aneurysm (MAA). The article assesses surgical practice, antibiotic therapy, outcome regarding survival and risk of infection related complications, along with risk factors associated with favourable and adverse outcomes. This study offers not only an overview of the management of MAAs, and demonstrates the limited scientific support for its current management, but also reveals how this could efficiently be addressed. Standardised reporting is needed to increase comparability of studies. Endovascular aortic repair appears to be associated with superior short term survival without late disadvantages, compared with open surgical repair.

Objectives: The aim of this systematic literature review was to compile an updated overview of mycotic aortic aneurysm (MAA) treatment and outcomes.

Methods: A systematic literature review was performed using the search terms mycotic and infected aortic aneurysms in the MEDLINE and ScienceDirect databases, published between January 2000 and September 2018. Using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, articles were scrutinised regarding surgical technique, aortic segment involved, pre- and post-operative antibiotic regimens, survival and infection related complications (IRCs), and factors associated with adverse or favourable outcomes.

Results: Twenty-eight studies, with a total of 963 patients, were included. All publications were observational, retrospective studies. Patient and study heterogeneity, along with missing data, precluded meta-analyses. Overall treatment consisted of open surgical repair (OSR; $n = 556$ [58%]), endovascular aortic repair (EVAR; $n = 373$ [39%]), and medical treatment alone ($n = 34$ [3%]). OSR was the dominant surgical technique prior to 2010, shifting to EVAR thereafter. For MAAs located in the abdominal aorta, EVAR was associated with better short term survival than OSR. Antibiotic treatment for more than six months post-operatively was associated with better survival, but there was no consensus on the length of treatment. MAAs were complicated by IRCs in 21%, irrespective of surgical technique, of which 46%–70% were fatal. The most consistently reported factors associated with adverse outcomes were increasing age, rupture, suprarenal abdominal aneurysm location, and non-*Salmonella* positive culture.

Conclusions: With few exceptions, the literature mainly consists of small, retrospective single centre studies. Standardised reporting is needed to increase comparability of studies. EVAR appears to be associated with superior short term survival without late disadvantages, compared with OSR. This suggests that EVAR can be an acceptable alternative to OSR. However, MAA treatment should always be tailor made and planned individually, and general recommendations are in vain. IRCs pose a significant threat to patients after MAA repair and require further investigation.

Keywords: Aneurysm, EVAR, Infected, Aorta, Mycotic, Review, Surgery, Treatment

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INTRODUCTION

The therapeutic management of mycotic aortic aneurysm (MAA) is challenging.[1] The incidence is approximately 0.6%–2% of all aortic aneurysms in Europe and the USA, and as high as 13% in Taiwan.[1–5] MAAs can develop anywhere in the aorta, with approximately 50% located above

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the renal arteries.[1,6] The majority of patients present with symptoms. The prognosis is generally poor, as the rapidly growing aneurysm has a high risk of rupture, and affected patients are often elderly with cardiovascular comorbidities and concomitant infections or sepsis.[7] Up to 2000, the reported peri-operative mortality was 26%—44%.[2,8—11]

The treatment of MAA consists of antibiotics and surgery, the latter either by open surgical repair (OSR), i.e. aneurysm resection with tissue debridement and revascularisation, or endovascular aneurysm repair (EVAR).[12] The first EVAR for MAA was reported in 1998.[13] Post-operatively, there is a risk of development of infection related complications (IRCs), but the precise risk is uncertain.[1,7] EVAR has been considered potentially more prone to IRCs as the stent graft is deployed in an infected field without resection of the infected nidus. Few studies report on conservative treatment with antibiotics only for MAA, and those that do demonstrate very poor results.[4]

The rarity of the disease implies that few centres acquire experience in managing these patients. Indeed, there remains a lack of consensus regarding diagnostic criteria and reporting standards. The heterogeneity of patients, causative bacteria, and anatomical distribution also make it difficult to accrue valid empirical evidence. Thus, despite the well known threat of mycotic aneurysm development, limited progress has been made in improving its treatment.

The aim of the present systematic literature review was to compile an overview of modern management of MAAs, looking specifically at surgical treatment of respective aortic segments and associated outcomes in terms of survival, IRCs, and antibiotic treatment and other factors associated with adverse or favourable outcomes.

METHODS

A systematic literature search was performed according to the PRISMA statement in the MEDLINE and ScienceDirect databases to identify all publications on MAAs in the English language between 1 January 2000 and 1 September 2018.[14] Search terms included “mycotic aortic aneurysm” and “infected aortic aneurysm”. Reference lists were also scrutinised to identify additional papers. Papers with duplicate cases were judged individually for inclusion, with the intention to include as many papers with as little patient overlap from previous reports as possible. At the same time, priority was given to the maintenance of patient homogeneity regarding anatomical location, i.e. studies reporting on MAAs with a specific aortic location, as opposed to a mixture of all aortic locations without subanalyses for the different aortic locations. The Newcastle—Ottawa scale (NOS) score was used for quality assessment by examining patient selection methods, comparability of groups, and assessment of outcome. Studies achieving at least seven of nine stars were judged to be of high quality. However, quality assessment was not used as an exclusion criterion.[15] Data were extracted for each paper according to a predefined protocol regarding medical history, clinical presentation (including symptoms, laboratory findings, concurrent infection), bacteriology, anatomical location, radiology findings, pre- and post-operative antibiotic treatment, surgical treatment of respective aortic segments (arch, descending, paravisceral, infrarenal, and iliac) and associated outcomes regarding survival and infection related complications, follow up (time), complications (including infection related complications), pre- and post-operative antibiotic treatment, and factors associated with adverse or favourable outcomes.

The following definition and diagnostic criteria for MAA were used: MAA is an aneurysm specific to the aorta as a result of infection, while the diagnosis is based on a combination of clinical presentation (pain, fever, concomitant infection, and patient with cardiovascular disease and/or immunosuppressed state), laboratory results (raised inflammatory parameters, including C reactive protein [CRP], white blood cell [WBC] count, and positive blood or aneurysm wall cultures), and corroborative imaging findings on computed tomography, such as saccular, eccentric, or multilobular aneurysm, peri-aortic mass, peri-aortic gas, and rapid aortic expansion. Thus, only one criterion did not suffice for the diagnosis of MAA, but a combination of at least two of the criteria listed above was required. Studies that did not include the diagnostic work up described above were excluded (Fig. 1). Aortic graft infections (AGI) and aorto-enteric fistulas (AEF) secondary to previous surgery were excluded, as well as studies with mixed cohorts of MAA and AGIs and AEFs. However if the AGI or the AEF developed as a complication of the MAA or its treatment, the study was included. Studies containing cases treated before 1990 were also excluded as well as a series consisting of fewer than 10 patients. CRP and WBC counts were presented as ranges. Post-operative IRC were defined as persistent or recurrent sepsis, graft or stent graft infection, recurrent MAA, or the development of aorto-enteric/bronchial fistula. Peri-operative mortality was defined as death in the early post-operative period. As some studies reported 30 day mortality, while others solely reported 90 day mortality after surgery, both these outcome measures were included in the data on peri-operative mortality. Short term survival was defined as survival for the first post-operative year. All eligible papers were read in full.

The primary data search was performed by one author (K.S.), in collaboration with university librarians, and the results were cross checked by the other authors (J.B.L., K.M., and A.W.). Data extraction and quality assessment were performed by one author (K.S.), and the results were, in turn, scrutinised by the other authors (J.B.L., K.M., and A.W.). If there was any disagreement between investigators, this was resolved by discussion until consensus was achieved (all authors). A statistician was consulted for meta-analysis calculations, which were not possible owing to the heterogeneity of the data.

RESULTS

Overall, 28 studies were included (Fig. 1).[5,16—42] Excluded studies that did not meet the pre-set inclusion criteria are

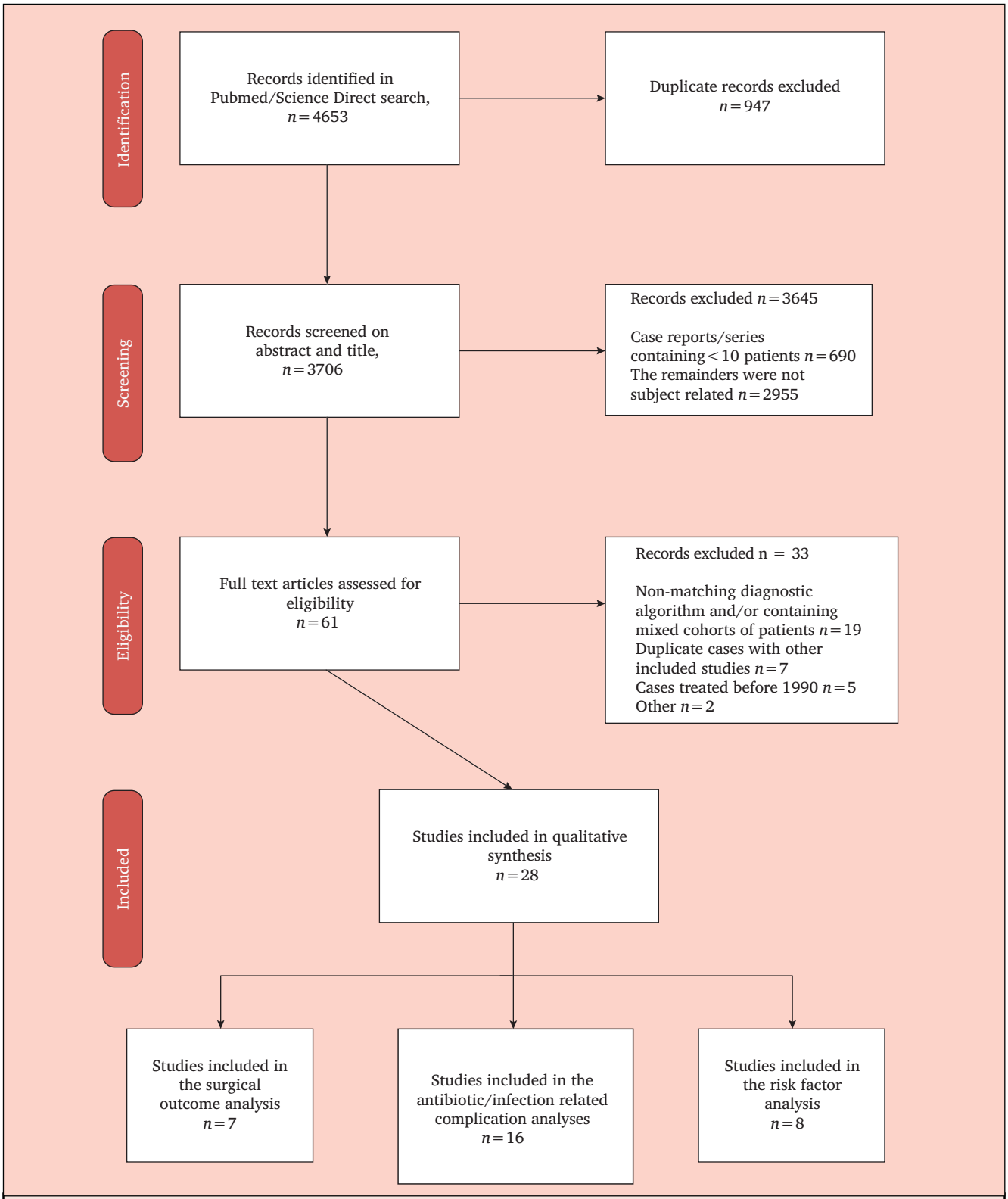

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.

listed in Table S1 (Supplementary Material). All but one study achieved a NOS score of $\leq$5 (see Table 1, and for details see Table S2 [Supplementary Material]). The individual study given a score of 8 was a large, multicentre and population based analysis from a prospectively collected and well validated registry, with good comparability and explicit outcome.

Owing to heterogeneous, descriptive publications with different endpoints, missing data, and an absence of odds ratios (ORs), it was not possible to carry out meta-analyses,

Table 1. List of included papers with respective quality score

Study	Country	Study design	Time period	Patient, *n* total (OSR/EVAR)	Median follow up − mo	Aim of study	Newcastle −Ottawa scale score
Fillmore, 2003[34]	USA	S-c. Retro.	1996−2002	10 (10/0)	17	Report results of experience	3
Luo, 2003[5]	Taiwan	S-c. Retro.	1993−1999	15 (15/0)	84	Report results of experience	3
Hsu, 2004[16]	Taiwan	S-c. Retro.	1995−2003	46 (46/0)	27	Report results on survival and risk factors	4
Kyriakides, 2004[17]	UK	S-c. Retro.	1991−2001	15 (15/0)	38	Report safety and efficacy of OR	3
Chen, 2005[18]	Taiwan	S-c. Retro.	1994−2004	17 (17/0)	37	Report results of experience	3
Hsu, 2008[19]	Taiwan	S-c. Retro.	1995−2007	32 (32/0)	16	Report results of *in situ* reconstruction	4
Woon, 2008[20]	Singapore	S-c. Retro.	1997−2006	18 (18/0)	34	Report results of experience	3
Clough, 2009[21]	UK	S-c. Retro.	1998−2008	19 (0/19)	20	Report results of EVAR for MAA	3
Kan, 2010[22]	International	S-c. Retro.	1990−2008	41 (21/20)	12	Report comparison on survival between OR and EVAR	4
Brossier, 2010[36]	France	S-c. Retro.	1992−2009	26 (24/2)	49	Report results of experience	3
Dubois, 2010[23]	Belgium	S-c, Retro.	1990−2008	44 (43/1)	53	Report results of experience	4
Vallejo, 2011[24]	UK	S-c. Retro.	2002−09	17 (9/8)	31	Report results of experience	3
Yu, 2011[25]	China	S-c. Retro.	1998−2007	56 (54/2)	42	Report results of experience	4
Hsu, 2011[26]	Taiwan	S-c. Retro.	1997−2010	14 (5/3)	30−52	Report results of experience	4
Kan, 2012[27]	Taiwan	M-c. Retro.	2007−11	12 (0/12)	24	Report results of EVAR	4
Sedivy, 2012[28]	Czech Republic	S-c. Retro.	1996−2010	32 (0/32)	45	Report results of EVAR	3
Uchida, 2012[29]	Japan	S-c. Retro.	2003−10	23 (21/2)	NS	Report results of *in situ* reconstruction	3
Jia, 2013[30]	China	S-c. Retro.	2001−10	12 (3/9)	17	Report results of experience	3
Lee, 2014[35]	Taiwan	S-c. Retro.	1998−2007	26 (26/0)	31	Report results of experience	4
Sörelius, 2014[31]	Europe	M-c. Retro.	1999−2013	123 (0/123)	35	Report survival after EVAR and complication rate	5
Huang, 2014[32]	Taiwan	S-c. Retro.	1997−2012	43 (29/11)	36	To identify risk factors for adverse outcome after surgical treatment	3
Lau, 2015[37]	USA	S-c. Retro.	1997−2014	14 (14/0)	27	Report results of experience	4
Sörelius, 2016[33]	Sweden	M-c. Retro.	1994−2014	132 (62/70)	39	Report comparison in survival between OR and EVAR in abdominal MAAs	8
Luo, 2017[38]	Taiwan	S-c. Retro.	2009−15	40 (0/40)	25	Report long term results after EVAR	4
Aoki, 2017[39]	Japan	S-c. Retro.	2002−15	26 (26/0)	76	Report results of experience	3
Nemoto, 2017[40]	Japan	S-c. Retro.	1995−2015	25 (25/0)	36	To identify risk factors for adverse outcome after surgical treatment	3
Kan, 2018[41]	Taiwan	S-c. Retro.	1993−2014	29 (14/15)	2−9	Report comparison in outcome between OR and EVAR in MAAs complicated by fistulation	5
Heinola, 2018[42]	International	M-c. Retro.	2006−16	56 (56/0)	26	Report results of OSR with biological grafts	4

OSR = open surgical repair; EVAR = endovascular aneurysm repair; S-c = single centre; Retro = retrospective study; M-c = multicentre; NS = not stated; OR = open repair; MAA = mycotic aortic aneurysm; mo = months.

or to assess publication bias properly. However, an assessment of the outcome of the identified studies in terms of mortality and frequency (%) of IRCs after mycotic aneurysm repair in different aortic segments was performed, and displayed as the range between studies at different time intervals, to provide an overview of surgical results.

Patient characteristics

The total number of patients in the 28 studies was 963. Mean patient age was 69 years, 73% were men, 74% had at least one cardiovascular comorbidity, and 44% presented with aneurysm rupture (Table 2). Approximately 60% of all the MAAs were located below the renal arteries. The most common symptoms at presentation were pain and fever (77% and 67%, respectively). Overall, 82% ($n = 602/734$) of the pathogens consisted of one of the following: *Salmonella* species (33.4% of the entire cohort), staphylococci (15.6%), streptococci (10.4%), and *Escherichia coli* (3.1%). For culture result details, see Table 3. The largest studies were from Europe and Taiwan, and these studies differed in culture results.[12,16,19,26,27,31–33,38] The most common pathogen in Taiwan was non-typhoid *Salmonella* (60% *vs.* 12%), while in Europe the most frequent pathogens were streptococci and staphylococci, which were the second and third most common pathogens in Taiwan.[16,19,26,31,33]

Management

Of the 963 patients, 556 (58%) were treated with OSR, 373 (39%) with EVAR, and 34 (4%) with antibiotics only (Table 2).

Surgical management. Until 2007, most published articles reported on the results of OSR. After 2007, there has been a steady increase in the number of patients treated by EVAR. Indeed, after 2008, all series but four in this literature review included patients treated by EVAR (Table 1). Table 4 summarises surgical technique and associated merged mortality at different time intervals post-operatively, as well as the rate of IRCs for each aortic segment from the aortic arch to the iliac vessels. The reported mortality varied depending on aortic segment involved and surgical approach. The 30–90 day mortality range for MAAs of the infrarenal aorta and iliac arteries was 3%–9% for EVAR and 5%–23% for OSR. Mortality data on MAAs of the thoracic aorta are less common, but the 30–90 day mortality range for the descending aorta was estimated at 15% for thoracic EVAR and 7%–20% for OSR.

Most authors recommended prompt surgery for all patients with MAA, irrespective of aneurysm size, although some advocated an algorithm based on the haemodynamic stability and progression or remission of symptoms. That is, stable patients who clinically responded well to immediate medical therapy were offered delayed surgical repair in order to allow maximum benefit of antibiotic treatment. Haemodynamically unstable patients, or those who had no remission of pain or fever, were otherwise offered prompt surgical repair.[16,19,22,26,32,35]

An analysis of a population based cohort of 132 patients with abdominal MAAs, where 50% were treated by OSR and 50% by EVAR, revealed a significant survival benefit for the EVAR cohort (97% *vs.* 73% [$p < .001$] at three months; 86% *vs.* 73% at one year).[33] Other than this paper, there is no face to face comparison regarding the outcome of different surgical techniques in MAA treatment.

OSR was performed with resection of the aneurysm and debridement of infected tissue, followed by revascularisation, performed by various techniques (*in situ* reconstruction or extra-anatomic bypass). Reported complications after extra-anatomic bypass included aortic stump blow out in two of 87 (2%) patients,[20,25] graft occlusion in four of 13 (31%) patients,[35] and subsequent claudication due to graft stenosis in eight of 22 patients (36%).[20,35] *In situ* reconstruction reported anastomotic dehiscence and bleeding in three of 324 patients (1%),[5,23,33] while data on graft occlusion/claudication could not be extracted. Series reporting on both extra-anatomic and *in situ* repair, reported

Table 2. Characteristics of 963 patients with mycotic aortic aneurysms based on the reviewed literature[a]

Patient characteristics	*n*/m (%)
No. of patients	963
Mean age ± SD – y	69 ± 5.0
Sex	
Female	257 (27)
Male	706 (73)
Concomitant or recent infection	219/495 (44)
History of cardiovascular disease	296/400 (74)
History of immunosuppressive state	321/777 (41)
Symptoms	
Pain	684/887 (77)
Fever	603/899 (67)
Shock	101/667 (15)
Median culture positive (range) – %	76 (34–100)
Laboratory findings – range	
CRP – mg/L	166–209
WBC – $\times 10^9$/L	12–16
Rupture	382/862 (44)
Aneurysm location	
Ascending	1/812 (0.1)
Arch	33/812 (4)
Descending	106/812 (13)
Suprarenal	116/812 (14)
Infrarenal	484/812 (60)
Iliac	17/812 (2)
Multiple	26/812 (3)
Surgical approach	
Open surgical repair	556/929 (60)
In situ repair	420/519 (81)
Extra-anatomical repair	90/519 (17)
Patch plasty	1/519 (0.2)
Endovascular repair	373/929 (40)
Hybrid repair	33/373 (9)
Only medical treatment	34/963 (4)
Infection related complications	168/820 (21)

Data are given as *n*/m (%), where m is total number of patients with available data, unless otherwise indicated.
CRP = C reactive protein; WBC = white blood cell count; SD = standard deviation; y = years.
[a] Data based on all 28 studies included in this systematic review.

Table 3. Positive culture results of patients with mycotic aortic aneurysms based on the reviewed literature[a]

Cultures (n = 734)	n (%)
Salmonella species	322 (33.4)
Staphylococcus species	150 (15.6)
Streptococcus species	100 (10.4)
Escherichia coli	30 (3.1)
Mycobacteria species	19 (2.0)
Enterobacter species	12 (1.2)
Klebsiella species	11 (1.1)
Campylobacter species	8 (0.7)
Clostridium species	7 (0.7)
Listeria species	7 (0.7)
Pseudomonas species	6 (0.6)
Proteus mirabilis	6 (0.6)
Bacteroides fragilis	6 (0.8)
Candida albicans	5 (0.5)
Haemophilus species	4 (0.4)
Serratia marcescens	2 (0.2)
Coxiella burnetii	2 (0.2)
Miscellaneous species with one positive culture	42 (4.4)
Negative cultures	224 (23.3)

[a] Data based on all 28 studies included in this systematic review.

fewer complications using *in situ* repair, with no increased risk of IRCs and lower 30—90 day mortality (50%—67% *vs.* 17%—19%); however, these are small, single centre studies and numbers were not statistically significant.[16,23,25,32,35] *In situ* reconstruction consisted mostly of synthetic conduits, in some cases antibiotic soaked grafts.[15—21,30,34—36] Only one publication fulfilling the inclusion criteria of the current study, presented results after OSR with miscellaneous biological grafts, demonstrating an estimated 90 day survival of 91%, and five year survival of 71%, and with no case of IRC.[43] The study was an international, multicentre study with low numbers of included patients per country and a low rate of ruptures (21%), indicating a possible selection bias to treatment.[42] Other publications reported results of deep vein conduits, i.e., neo-aorto-iliac system, silver coated polyester graft, or cryopreserved homografts, but only in individual patients.[34,36] There was no evidence regarding the superiority of one prosthetic material over another. The use of *in situ* reconstruction with omental pedicle wrapping has been reported with few IRCs (n = 1/147 [0.7%]).[5,29,37] Additional use of systematic irrigation of the abdomen has been reported by Nemoto *et al*. with promising results.[40]

Reports on endovascular repair have mostly consisted of standard EVAR treatment. They have, however, also included cases of fenestrated and branched repair of suprarenal and thoraco-abdominal aneurysms, as well as hybrid repair with supra-aortic or visceral artery deviation followed by endovascular repair.[28,31—33] Although EVAR for MAA often did not include local debridement of the infected field, EVAR was not associated with a higher rate of IRCs (24% *vs.* 18%, p = .439) or re-operations (24% *vs.* 21%, p = .650) when compared with OSR for abdominal MAAs in one study.[33]

Antibiotic treatment. Two studies also included patients treated exclusively medically, reporting an in hospital mortality rate of 75%—100%, with all deaths due to aneurysm rupture.[32,35] Pre-operative antibiotic therapy ranging from two to six weeks has been reported to be standard practice in Taiwan, unless emergency surgery is indicated.[16,19,22,26,27,32,35] The variety of post-operative antibiotic treatment strategies varied from absent to four to six weeks, to a minimum of three to six months, to six to 12 months, and to lifelong, and to be assessed on an individual case by case basis. Table S3 summarises different pre- and post-operative antibiotic regimens and recommendations. Pre-operative antibiotic treatment for more than three days had an OR of 0.2 (95% confidence interval [CI] 0.04—0.96) for aneurysm related mortality and morbidity,[22] and

Table 4. Reported mortality after repair of mycotic aortic aneurysm in different aortic segments for both open surgical repair (OSR) and endovascular aortic repair (EVAR)

Aortic segment	Mortality 30—90 days — %	Mortality 1 year — %	Mortality 5 years — %	IRC — %	No. of patients	Reference(s)
Arch						
OSR	10—60	50		20	15	Hsu, 2008;[19] Yu, 2011[25]
EVAR	25	25	25	25	4	Sörelius, 2014[31]
Descending						
OSR	7—20	29	29	0—33	38	Hsu, 2008;[19] Yu, 2011;[25] Lau, 2015[37]
EVAR	15	24	40	32	34	Sörelius, 2014[31]
Paravisceral						
OSR	20—60	20—50	67	0—20	18	Hsu, 2011;[26] Yu, 2011;[25] Sörelius, 2016[33]
EVAR	11—33	22—66	63—68	0—33	27	Hsu, 2011;[26] Sörelius, 2014;[31] Sörelius, 2016[33]
Infrarenal						
OSR	5—23	23	36	21—44	94	Kan, 2010;[22] Yu, 2011;[25] Sörelius, 2016[33]
EVAR	3—9	10—14	37—41	20—25	120	Kan, 2010;[22] Sörelius, 2014;[31] Sörelius, 2016[33]
Iliac						
OSR	0				3	Yu, 2011[25]
EVAR	0	0	23	0	3	Sörelius, 2016[33]

IRC = infection related complication; OSR = open surgical repair; EVAR = endovascular aortic repair.

another study demonstrated post-operative antibiotic duration of more than six months to have a hazard ratio of 0.36 (95% CI 0.18–0.74, $p = .005$) for late mortality in multivariable analysis.[33]

Infection related complications. A range of post-operative IRCs (sepsis, graft/stent graft infections, recurrent MAAs, and aorto-enteric fistulas) were reported after both OSR and EVAR (see Tables 4 and S2). The incidence varied with notable differences in length of follow up and aortic segment involved. The overall incidence was 21% ($n = 168/820$) in the included studies, while 46%–70% were ultimately fatal.[31,33,38] Nearly 90% of all IRCs occurred within the first post-operative year, within a mean of three months.[31,33,38] MAAs complicated by aorto-enteric and aortobronchial fistulas had a particularly poor prognosis, with a reported mortality ranging between 63% and 100%.[21,22,25,33] Nemoto *et al*. reported no cases of IRCs when combining *in situ* reconstruction with extensive debridement, rifampicin soaked grafts, omental coverage, and additional use of routine irrigation with a so called Pulsavac.[40] Kan *et al*. investigated MAAs complicated by aorto-oesophageal or aortobronchial fistulation in 29 patients treated between 1993 and 2014.[41] Those patients treated by an endovascular approach demonstrated an estimated 30 day survival of 93% *vs*. 57% for OSR ($p = .035$). This survival benefit was still significant at six months ($p = .016$), but could not be detected at four years.

Prognostic factors

Although most publications were underpowered, risk factor analyses were performed in some studies. Factors associated with both favourable and worse outcomes are summarised in Table 5.

DISCUSSION

There are several important findings from this systematic literature review of MAA treatment: (i) the rarity of the disease and the heterogeneity of patients, treatments, and means of reporting preclude any attempts of meta-analyses; (ii) there is no high quality evidence to support either OSR or EVAR as the primary repair strategy, although EVAR seems to be associated with superior survival *vs*. OSR in MAAs with an abdominal location; (iii) post-operative antibiotic treatment for more than six months is associated with better outcomes; (iv) the above noted limitations reflect the fact that development of reporting standards is badly needed; and (v) that multicentre collaboration is necessary to obtain sufficient material for meaningful analyses.

In a complex disease such as MAA, the surgical solution needs to be tailored to each case. A minimally invasive surgical approach such as EVAR in elderly, comorbid patients with anatomically challenging MAAs is therefore a valuable option. This strategy was first adopted in non-infected aneurysms.[44] Open and endovascular procedures constituted 60% and 40%, respectively, of all MAAs included in this study. However, over the last 10 years the numbers have almost reversed, indicating a paradigm shift in the treatment of this disease.

The data regarding survival suggest that survival has improved over the past two decades (Table 4), and at least for infrarenal MAAs this is probably the case, although it is futile to attempt comparisons. Possible explanations include advances in intensive care and antibiotic regimens. However, the introduction of EVAR may also have played a role in this improvement. As shown in the national Swedish report, EVAR was associated with a clearly superior survival up to four years after surgery, without increasing the risk of IRCs or re-operation.[33] The Swedish survival figures for EVAR have been re-iterated in recent smaller studies.[10,27] Survival after OSR is superior to the Swedish data in some reports,[29,40] and in some not.[23] However, the quality of all these studies is poor, and there is no reliable comparison made between EVAR and OSR. IRCs develop in approximately 20% of all patients treated, with a 46%–70% mortality rate, seemingly irrespective of surgical technique. As there is no evidence to support OSR as a superior surgical approach, it is unclear why the American Heart Association (AHA) document from 2016 does not recommend EVAR as a surgical option for MAA, doing so only in the situation of rupture and uncontrolled bleeding.[1] The recently published European Society for Vascular Surgery (ESVS) 2019 Clinical

Table 5. Factors associated with favourable or adverse outcomeof patients with mycotic aortic aneurysms based on the reviewed literature

Author, publication year	Risk factor associated with death/adverse outcome	Protective factor associated with better outcome	Surgical approach	No. of patients in study
Hsu, 2004[16]	Age, non-*Salmonella* infection, no surgery	—	OSR	46
Kan, 2010[22]	Age, *Salmonella*, leukocytosis	Pre-operative Abx >3 d	OSR/EVAR	40
Yu, 2011[25]	Suprarenal aneurysm	—	OSR/EVAR	56
Sörelius, 2014[31]	Age, non-*Salmonella* infection	—	EVAR	123
Lee, 2014[35]		Surgery, abdominal pain	OSR	
Lau, 2015[37]	Chronic renal insufficiency, diabetes, NYHA class		OSR	14
Sörelius, 2016[33]	On short term: OR; long term: age, rupture, suprarenal aneurysm	Postoperative Abx >6 mo	OSR/EVAR	132
Luo, 2017[38]	Development of infection related complications	Negative culture	EVAR	40

OSR = open surgical repair; Abx = antibiotic treatment; EVAR = endovascular aortic repair; NYHA = New York Heart Association.

Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms stand in contrast to the recommendations by the AHA regarding surgical treatment of MAA.[45] The ESVS guidelines recommend that the surgical repair is based on patient status, local routines, and experience, with EVAR being an acceptable alternative to OSR (Class IIa, Level of Evidence C). The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm published in 2018 do not address the disease entity of MAA at all.[46]

It is difficult to make firm conclusions regarding antibiotic treatment, as reported regimens are diverse. Nonetheless, it appears beneficial to prolong antibiotic treatment 6—12 months post-operatively, irrespective of the surgical approach, and in some cases lifelong, especially in patients with a non-*Salmonella* positive culture. The AHA recommends a post-operative duration of six weeks to six months of antimicrobial therapy (Class IIb, Level of Evidence B); in some cases lifelong therapy may be considered, and the ESVS recommends 6—12 months or lifelong with surveillance (Class IIa, Level of Evidence C). In cases of *Salmonella* positive culture, the required length of antibiotic therapy may be reduced, owing to seemingly fewer IRC events after successful treatment. Considering the high risk of IRCs, involvement of infectious disease experts in the decision making regarding antibiotic management of patients with MAA is warranted. It is interesting to note that 23% of patients had negative cultures. This is probably an underestimate, as some of the included studies used positive culture as part of requisite diagnostic criteria.[5,16,22,27,32,35] The frequency of negative cultures, ranging from 25% - 33% in studies where a positive culture is not a prerequisite, is in accordance with culture rates of infective endocarditis.[47,48] The use of 16S ribosomal RNA gene analysis has yet to be evaluated for MAAs, but may prove to be a valuable tool in diagnosing and treating patients with negative cultures.[47]

As all included studies were retrospective and mostly single centre, the clinical interpretations of this systematic review must be taken with discretion. The summary of prognostic factors, for example, is particularly susceptible to type II statistical errors. There were challenges in the paper selection for this systematic review, and two specific cases need further explanation. The paper by Heinola *et al*.[42] had a 20% patient overlap with that of Sörelius *et al*.,[33] but it was included as the risk of bias was considered to be larger if had been excluded. A large Taiwanese study by Lin *et al*.[4] was excluded because of duplicate cases in favour of former, smaller publications from the same research group with less patient overlap but with more detailed surgical data for MAAs with homogenous anatomical locations.[16,19,26] The lack of consensus regarding diagnostic criteria is a glaring deficiency in the MAA literature, although the criteria were rather similar in the included studies. It is the opinion of the authors that a consensus document would be a major step in the improvement of the understanding and treatment of MAAs.[49]

Future improvements in treatment may include development of microbe resistant stent grafts, as well as improved antibiotic bonded stent grafts. Improved medical and, in particular, new antibiotic therapies, should also play a role. Finally, patient and bacteria specific algorithms regarding the timing and technique of repair may also prove to be more appropriate and effective.

The fact that no meta-analyses were possible to perform is a problem. An assessment of selection bias would have been particularly informative, as there may be a difference in patient selection, e.g. OSR for haemodynamically stable patients with fewer comorbidities. Data from the Swedish registry suggest that, as of 2007, significantly more patients are now offered surgical treatment, essentially enabled by the less invasive endovascular approach.[33,50] Hence, selection bias might reduce the observed survival benefit of EVAR *vs.* OSR. As management of rare diseases does not lend itself well to evaluation using standard surgical technique development tools,[51,52] reporting standards are warranted to overcome this issue. No randomised controlled trials in the treatment of MAAs have been performed for a number of reasons, the most important being the rarity and heterogeneity of the disease. Additionally, a randomised controlled trial would require a multinational study over many years, and maintaining equipoise in standard management would be difficult. However, a multi-institutional prospective study in accordance with pre-specified diagnostic criteria, antibiotic regimens, and standardised follow up is not insurmountable and might offer answers to many clinical questions.

CONCLUSION

With few exceptions, the literature mainly consists of small, retrospective single centre studies. Standardised reporting is needed to increase study comparability. EVAR appears to be associated with superior short term survival, without late disadvantages, compared with OSR. This suggests that EVAR can be an acceptable alternative to OSR. MAA treatment should always be tailor made and planned on a case by case basis, thus general treatment recommendations that apply to every patient are in vain. Multi-institutional collaborations are also essential for increased knowledge on optimal surgical care. Further research on antibiotic treatment is needed for recommendations to reduce the risk of IRCs, which currently pose a significant threat to patients after MAA repair and require further investigation.

CONFLICTS OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.05.004.

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COUP D'OEIL

Atrophie Blanche (C4b) Can Be Reversible After Targeted Treatment

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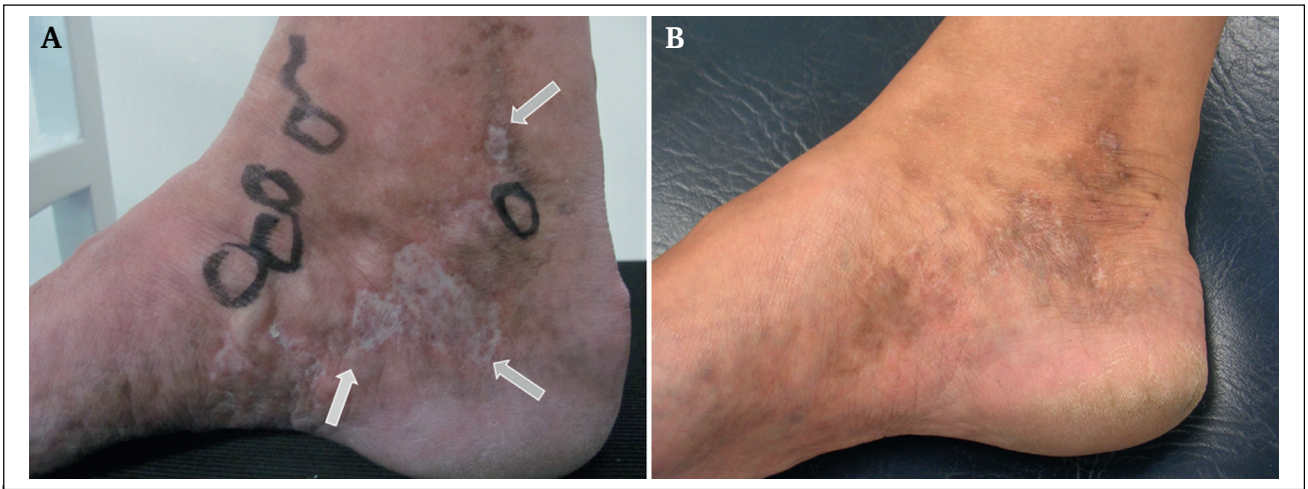

A 51 year old female teacher presented with complaints of heaviness and nocturnal cramps in the right leg eight years after high ligation and stripping of the great saphenous vein. Clinical examination revealed recurrent varicose veins, most prominent over the medial malleolus and foot (Panel A, marked black on the skin), where a large area of atrophie blanche was seen (arrows). Duplex ultrasound showed incompetence of the small and great saphenous veins and their tributaries. One year after radiofrequency ablation and phlebectomies, followed by additional foam sclerotherapy at the medial malleolus six weeks later, the atrophie blanche had recovered almost completely (Panel B).

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