On the Diagnosis of Mycotic Aortic Aneurysms

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ABSTRACT

OBJECTIVE: There is striking paucity in consensus on the terminology, definition, and diagnostic criteria of mycotic aortic aneurysms. This literature study aims to elucidate this scientific omission, discuss its consequences, and present a proposition for reporting items on this disease.

METHODS: A systematic literature review on PubMed and Medline using *mycotic* and *infected aortic aneurysms* between 1850 and 2017 was performed. Articles were assessed according to a protocol regarding terminology, definition, and diagnostic criteria. Case series with less than 5 patients were excluded.

RESULTS: A total of 49 articles were included. The most prevalent term was mycotic aortic aneurysm but there was no widely accepted definition. Most modern publications used a diagnostic workup based on a combination on clinical presentation, laboratory results, imaging findings, and intraoperative findings. How these protean variables should be balanced was unclear. A proposition of reporting items was framed and consisted of definition of disease used, basis of diagnostic workup, exclusion criteria, patient characteristics, laboratory and imaging findings, aneurysm anatomy, details on treatment, pre/postoperative antibiotic treatment, and details on follow-up.

CONCLUSIONS: This article emphasizes the need to standardize definition, terminology, and diagnostic criteria for mycotic aortic aneurysms and proposes reporting items enhancing comparability between studies.

KEYWORDS: Mycotic, aneurysm, infected, aorta, diagnosis, revised, terminology, criteria, reporting standards

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Introduction

A mycotic aortic aneurysm (MAA), synonymously known as infected aortic aneurysm, is an aortic aneurysm due to infection. Mycotic aortic aneurysm most commonly develops through microbial inoculation of the diseased aortic endothelium during bacteremia.[1,2] Once the microorganism has infected the aortic wall, a fast degradation of the intimal and medial layers may occur, with development of an aneurysm.[3–6] The causative infective agents are predominantly bacteria but rare cases of fungus have been reported.[7–9] The term "mycotic aneurysm" is thus a misnomer for infection, and imprecise, while implicating a fungal genesis, which is extremely rare. The term *mycotic* originates from 1885, when Sir William Osler, in his *Gulstonian lectures*, described a patient with valve vegetations and 4 aortic aneurysms with morphological fungal resemblance.[10] The term has since stuck, probably because of common usage. Osler was, however, not the first to describe the relationship between infective endocarditis and aneurysm development; Koch in 1851, Tufnell in 1853, and Oggle in 1866 were before him, but not for aneurysms involving the aorta.[11–13] Many have argued that a more correct term would be infected aortic aneurysm.[14–16] Throughout the past 130 years, the disease MAA has gone through significant changes; in the days of Osler, most of the aneurysms due to infections were secondary to syphilitic aortitis engaging the adventitia, with aneurysm formation at necrotic focal points due to obliterative endarteritis,[5,17] or infective endocarditis with septic embolization to the aorta,[5,14] whereas after the 1940s and the introduction of antibiotics, bacteremia in an aged atherosclerotic aorta is the dominant pathogenetic pathway.[18,19]

A plethora of terms such as "mycotic aneurysm", "primary mycotic aneurysm", "suppurative arteritis", "cryptogenic mycotic aneurysm", "SAP (septic aortic pseudoaneurysm)", and "infected aneurysm" have been used[14,20–24] but none with broad acceptance. It is also not uncommon in the literature to mix different infectious conditions involving the aorta, such as graft infection and aorto-enteric fistula together with aortic aneurysms due to infection.[25–27]

There are several problems when studying MAAs such as (a) ill-defined disease, (b) variable terminology indicating fungal genesis, (c) variable or absent diagnostic criteria in the literature, and (d) mixed patient populations with different aortic infections with different natural courses, with various demands on management.

The disease is rare, with an estimated incidence of 0.6% of all aortic aneurysms in Western countries[28,29] and up to 13% in Taiwan.[23] Hence, most existing studies are underpowered and

nonattainable for statistical inference. These problems, (a) to (d), make comparisons between studies unnecessarily challenging and sometimes impossible.

This article aims to elucidate the absence of definition and classification of MAAs, to discuss the consequences of lack of standardization, and to present a suggestion for reporting items to facilitate comparability between studies.

Methods

A systematic literature search was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement on PubMed and Medline between January 1, 1850 and January 1, 2017. The search terms were *mycotic aortic aneurysm* and *infected aortic aneurysm*. Reference lists were also scrutinized to identify additional papers. The ones discussing or introducing new terminology, definitions, diagnostic criteria, and classification were selected for scrutiny. Case series of at least 5 patients were read in full to analyze the diagnostic workup of the study. Case reports were not included. Graft infection and aorto-enteric fistulas were excluded. All selected studies were reviewed according to a predefined protocol regarding terminology, definition, diagnostic criteria, and classification of the disease.

Based on previous definitions, current knowledge on the disease, and present clinical needs, a proposition was framed for reporting items to account for when reporting on the disease.

Meta-analyses were not possible to perform due to the qualitative nature of the study, neither was risk of bias assessment.

Results

A total of 49 articles were included in the literature analysis, see flowchart in Figure 1. Whether the disease is increasing is unclear, but the number of publications has doubled per decade on mycotic/infected aneurysms between 1982 and 2012.[30]

Terminology and definitions

Table 1 lists different terms being used throughout history with accompanying definitions, diagnostic criteria, or significations attributed to aortic aneurysms caused by infection. The terms infective vasculitis and endovascular infection have mainly been used in the context of intracranial aneurysms due to infection. Since the 1980s, the most prevalent terms have been *mycotic* and *infected* aortic aneurysms. The most common definition was not evaluable due to too much diversity.

Pathophysiology and subclassifications

It has been recognized that MAAs might arise from different causes, see Table 2.[1–6,9] The table is a modified version of Wilson et al[36] from 1978. In addition to the Wilson classification, one more group has been added, ie, HIV-related aneurysms. These aneurysms are seen in young patients with advance-stage HIV infection, median age of 30 years with multiple aneurysms throughout the arterial system, and so far they have only been reported from the province of KwaZulu-Natal in the Republic of South Africa. The precise pathogenesis is unclear but there is to date no evidence of direct viral action leading to arterial wall destruction.[42] However, viral infection cannot be excluded as the pathogenetic pathway.

Diagnosis

Different criteria for aneurysms due to infection have been in use (Table 1). In the past 15 years, the diagnosis MAA has been based on a various combination of the following 4 criteria: (1) clinical presentation (pain, fever, concomitant infection, elderly patient with cardiovascular disease, and/or immunosuppressive state); (2) laboratory findings (raised inflammatory parameters including C-reactive protein [CRP], leukocytosis, and positive culture); (3) radiological findings on computed tomography (CT) or magnetic resonance imaging (saccular, eccentric, or multilobular aneurysm, periaortic mass, periaortic gas, and rapid aortic expansion) (Figure 2); and (4) intraoperative findings. One of the criteria is solely not sufficient for the diagnosis. However, there is no algorithm for making the diagnosis. Whether a positive blood culture is a prerequisite for the diagnosis or not is a point of disagreement.[24,55–57,61] Argument for positive culture being requisite, either in blood or tissue, is that it is the only way to certify an infectious pathophysiologic mechanism. Arguments against a positive culture being requisite are that it is known that these aneurysms yield a positive blood or tissue culture in only approximately 50% to 75% of the cases, even if harvested from the aneurysm sac with evident infection intraoperatively. This could be explained by difficulties in obtaining anaerobic cultures or initial broad-spectrum antibiotic therapy.[43,62,63] Also, if treated endovascularly, a tissue culture may not be obtained.[24] Older studies have demonstrated that routine culture of abdominal aortic aneurysm wall during surgery of clinically noninfected patients may be positive in 14% to 37%, which adds further complexity to this issue.[64–66] The value of positron emission tomography (PET) and granulocyte scintigraphy has not been evaluated properly but could probably aid in diagnostics in uncertain cases.

Most authors make clear distinction between an aneurysm due to infection and aorto-enteric fistulas and graft infections.

Proposition for reporting items

To facilitate comparisons between studies on MAA the following 10 essentials would preferably be accounted for:

1. Definition of disease and basis of diagnostic workup;
2. Exclusion criteria;
3. Patient characteristics (medical history: eg, cardiopulmonary disease, immunosuppressive states, or medication; data on presentation: symptoms, concurrent infection);
4. Laboratory results (inflammatory markers: CRP, levels of leukocytes, cultures from blood/tissues, results of polymerase chain reaction for bacteria identification);

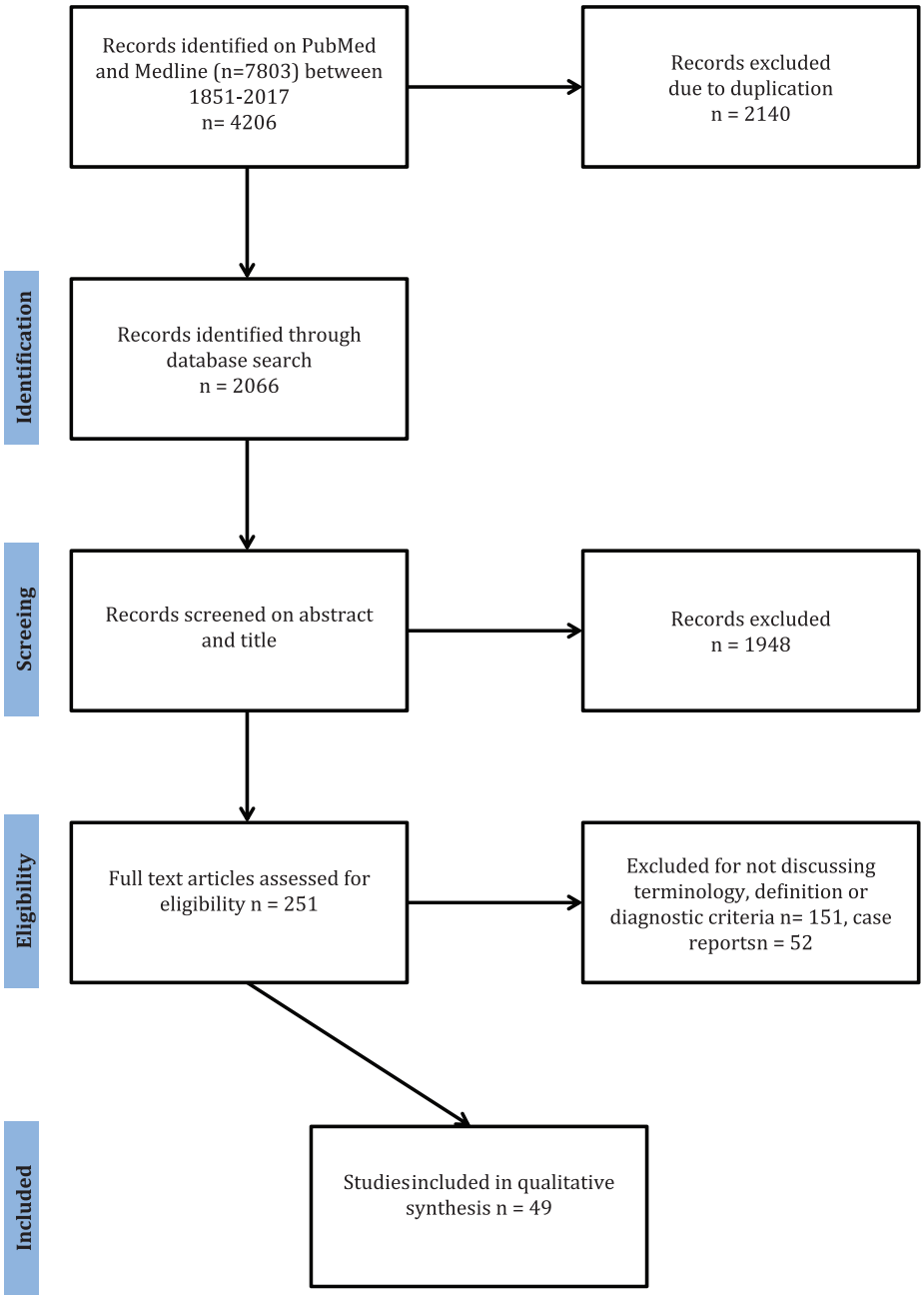

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Consort flow diagram.

5. Imaging findings and imaging modality (saccular or multilobular aneurysm, rapid expansion, periaortic gas formation within the aneurysm thrombus, periaortic soft tissue mass);
6. Aneurysm anatomy (level of aorta engaged);
7. Details on treatment (open repair; in situ bypass or extra-anatomic bypass and graft material: endovascular aortic repair; type of stent graft, hybrid procedure);
8. Preoperative antibiotic treatment time;
9. Postoperative treatment time (intravenous and oral);
10. Follow-up (time, symptoms, lab results, imaging modality, outcome, bacteriology in case of infection-related complication, reoperation—why, when, how, and result thereof).

Discussion

What is unclearly said, is unclearly thought

Esaias Tegnér, 1782-1846, member of the Swedish academy and professor in Greek.

Mycotic aortic aneurysms are extremely rare, making the disease difficult to study and statistical analyses problematic. Meanwhile, its management is very demanding and carries high mortality.[28,29,67] It is obvious that the terminology, definition, and diagnostic criteria of MAA are confusing. This confusion complicates comparisons between case series when this is necessary because collecting cases of MAA is a major undertaking and evidence-based treatment is lacking. An explicit definition with coherent terminology and

Table 1. Account of the plethora of terminologies, definitions, diagnostic criteria, and significance attributed to aortic aneurysms due to infection.

AUTHOR (YEAR OF PUBLICATION)	TERMINOLOGY	DEFINITION (D), DIAGNOSTIC CRITERIA (DC), SIGNIFICATION, OR UNDERSTANDING OF THE DISEASE
Oggle (1866)[13]	—	Proposing relationship between aneurysms and endocarditis
Osler (1885)[10]	Mycotic aneurysm	Aneurysm associated with infective endocarditis
Eppinger (1887)[31]	Embolomycotic	Infectious and embolic etiology of aneurysm
Wiesel (1906)[32]	—	Not all aneurysms due to infection are related to endocarditis, but to infection in general
Lewis (1909)[33]	Embolomycotic aneurysm	D: Causes of aneurysm due to infection were not solely endocarditis but also trauma and other infection
Stengel (1923)[3]	Mycotic (bacterial) aneurysms	Mycotic aneurysms may arise without endocarditis, and cultures are difficult to determine
Crane (1937[20]	Primary multiocular mycotic aneurysm of the aorta	D: Lesion developed in the aortic wall without associated intravascular focus, no intra/extravascular inflammation or endocarditis
Barker (1954[34]	Mycotic aneurysm	Recommending prompt surgery
Parkhurst (1955)[5]	Mycotic (bacterial) aneurysm of the aorta	Preexisting disease of the aorta favors establishment of infection
Sommerville (1959)[1]	Infected arteriosclerotic aortic aneurysm	Preexisting aneurysms may be secondarily infected
Blum (1962)[21]	Cryptogenic mycotic aneurysm	Bacteria invading the endothelium at the site of atherosclerotic disease
Sower (1962)[35]	Suppurative arteritis	—
Bennett (1967)[4]	Bacterial infection of aortic aneurysm	—
Jarrett (1975)[14]	Infected aortic aneurysm	Objecting the term mycotic since indicating a fungal genesis
Patel (1977)[22]	Mycotic aneurysm	Switch of terminology. D: New classification; consider preexisting arterial status and source of infection, excluding infected preexisting aneurysms, intracranial aneurysms and infected prostheses
Wilson (1978)[36]	Spontaneous arterial infections	D: Classification and subgroups: mycotic aneurysms, infected aneurysms, microbial arteritis, traumatic infected pseudoaneurysm
Davies (1978)[37]	Cryptic mycotic abdominal aneurysm	DC: Combination of fever, pulsatile mass and aortography
Johansen (1983)[38]	Mycotic aortic aneurysm	Recognizing a substantial part of patients suffer from immune suppression
Oz (1989)[39]	Bacterial aortitis	Emphasizes that aortas of normal diameter may be infected
Chan (1989)[40]	Mycotic aneurysm of the aorta	Naturally occurring aortic aneurysms that result from or are secondarily infected by bacteria arising in a distant site of infection
Reddy (1991)[18]	Infected aortoiliac aneurysm	D: Retaining the Wilson classification, and adding a subgroup of aortic infection due to contiguous spread from adjacent organ
Fichelle (1993)[a,41]	Infected aortic aneurysm	D: Subclassification: postembolic aneurysms, infective aortitis, infected atherosclerotic aneurysms. Including aortic fistulas
Sessa (1997)[a,16]	Infected aneurysm	D: A lesion of the arterial wall due to bacterial contamination
Nair (2000)[42]	HIV-related aneurysms	Description of multiple aneurysms in young patients with advanced HIV infection
Müller (2001)[43]	Mycotic aneurysm	DC: Positive culture (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
Ihaya (2001)[44]	Infectious aortic aneurysm	—

Table 1. (Continued)

AUTHOR (YEAR OF PUBLICATION)	TERMINOLOGY	DEFINITION (D), DIAGNOSTIC CRITERIA (DC), SIGNIFICATION, OR UNDERSTANDING OF THE DISEASE
Oderich (2001)[45]	Infected aortic aneurysm and primary aortic infection	DC: Combination of operative findings, clinical infection, and positive aneurysm culture
Luo (2003)[23]	Septic aortic pseudoaneurysm	D: Aortic pseudoaneurysm caused by infection with or without bacteremia, excluding fusiform aneurysms
Jones (2004)[a,25]	Mycotic aortic aneurysm and infected false aneurysm	No definition. Including aorta-bronchial, aorto-esophageal and aorto-cutaneous fistulas, which had previous thoracic aortic grafts
Kyriakides (2004)[a,46]	Mycotic aortic aneurysm/primarily infected aortic aneurysm	Unclear definition, however excluding prosthetic graft infections, arterial infection secondary to trauma and aneurysms with positive routine culture
Hsu (2004)[47]	Primary infected aortic aneurysm	DC: Combination of clinical signs of infection, imaging findings on CT or MR, aortic aneurysm >3 cm, and positive culture
Kuniyoshi (2005)[a,48]	Mycotic aortic aneurysm	DC: Aneurysm morphology or intraoperative findings
Chen (2005)[a,49]	Mycotic aortic aneurysm	DC: Positive culture from the aneurysm wall or pus surrounding the aneurysm if negative culture from the aneurysm
Tiesenhausen (2007)[50]	Mycotic aortic pseudoaneurysm	DC: Clinical picture of infection, positive blood culture, aortic imaging
Razavi (2008)[a,51]	Mycotic aneurysm	Unclear definition and diagnostic criteria
Hsu (2008)[52]	Infected aortic aneurysm	DC: Combination of clinical signs of infection, imaging findings on CT or MR, aortic aneurysm >3 cm, and positive culture
Clough (2009)[a,53]	Mycotic aortic aneurysm	D: All aneurysms of infective etiology
Sörelius (2009)[24]	Mycotic aortic aneurysm	DC: Combination of clinical signs of infection, hematologic tests and culture, and imaging. Positive culture not requisite.
Dubois (2010)[54]	Mycotic aortic aneurysm	DC: Combination of clinical signs, imaging, intraoperative findings, positive aneurysm culture. Recent infection was also taken into account if negative culture
Kan (2010)[55]	Mycotic aortic aneurysm	DC: Combination of clinical course with infectious signs, positive blood or tissue culture and aortic imaging
Hsu (2011)[56]	Infected aortic aneurysm	DC: Combination of clinical signs of infection, imaging findings on CT or MR, aortic aneurysm >3 cm, and positive culture
Kan (2011)[57]	Infected aortic aneurysm	Author switching terminology, but retaining diagnostic criteria: combining clinical course with infectious signs, positive blood or tissue culture, and aortic imaging
Yu (2011)[58]	Mycotic aortic aneurysm	DC: Combination of clinical signs of infection, characteristic imaging, and intraoperative inflammation or purulence
Bisdas (2011)[15]	Infected aneurysm	Supporting the Wilson classification, and arguing for a change of terminology
Sedivy (2012)[59]	Infected aortic aneurysm	Definition according to Wilson, diagnostic criteria unclear but excluding graft infections and fistulas, and positive culture is not a requisite
Uchida (2012)[60]	Mycotic aortic aneurysm	DC: Combination of clinical, imaging and pathological evidence
Lin (2014)[8]	Primary infected aortic aneurysm	DC: Combination of clinical signs of infection, imaging findings on CT or MR, aortic aneurysm >3 cm, and positive culture
Sörelius (2014)[61]	Mycotic aortic aneurysm	DC: Combination of clinical signs of infection, hematologic tests and culture, and imaging. Positive culture not requisite
Sörelius (2016)[29]	Mycotic aortic aneurysm	DC: Combination of clinical signs of infection, hematologic tests and culture, and imaging. Positive culture not requisite

diagnostic criteria needs to be settled. It is a fundamental process to standardize everything from definition, terminology, and methodology within science, and the discipline of vascular surgery should be of no exception. This would facilitate research, elevate the level of knowledge, make comparative analyses simpler, and enable development of treatment guidelines. Many authors prefer the term mycotic because of common usage, but if retained, it should be made

Table 2. Amended classification of aortic aneurysms caused by infection according to Wilson et al,[36] "Spontaneous arterial infections."

	MYCOTIC ANEURYSM	INFECTED ANEURYSM	MICROBIAL ARTERITIS	TRAUMATIC INFECTED PSEUDOANEURYSM	HIV-RELATED ANEURYSM[a]
Etiology	Endocarditis	Bacteremia	Bacteremia	Trauma/punction	HIV
Sex	F>M	M	M	M or F	M
Age	30-50	More than 50	More than 50	Less than 30	Around 30
Incidence	Rare	Unusual	Common	Common	Unusual
Location	Any vessel	Distal aorta	Aortoiliac	Femoral, carotid	Any vessel
Number	Multiple	Single	Single	Multiple	Multiple
Bacteriology	Gram-positive cocci	*Staphylococcus aureus, Escherichia coli*	*Salmonella* sp.	Polymicrobial	

The last column "HIV-related aneurysm" was added by the authors of this article.

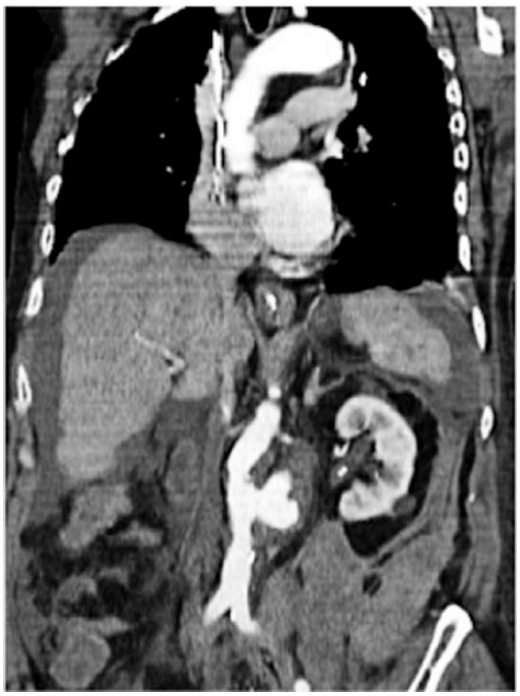

Figure 2. A mycotic abdominal aortic aneurysm.

explicit what the term alludes. Or, if both infected and mycotic could be used synonymously, that should be made clear as well.

It is important to distinguish MAAs from secondary aortic infections, such as graft infections, secondary aorto-enteric fistulas, and also inflammatory aneurysms, IgG4-related inflammatory aneurysms, and penetrating aortic ulcers because of differences in natural history and demand on management.[2,8,28,29,68,69] A consensus document would be welcome as both the Society for Vascular Surgery (SVS) and the European Society for Vascular Surgery (ESVS) lack guidelines in treatment of MAAs. There is also a demand on evidence-based treatment guidelines because there are indications that the incidence of MAA is increasing.[30,61]

However, there may be many challenges defining MAAs, for example, the morphological characteristics of the aneurysm will probably matter. Most MAAs are saccular, but what is a saccular aneurysm? There is no distinct definition of *saccular* aneurysm either; should the diameter matter, and how should it be measured?

The same work remains for graft infections and aorto-enteric fistulas. The work by the MAGIC group is an important, encouraging step in the right direction, where a diagnostic algorithm was constructed for aortic graft infection by a multidisciplinary panel of experts.[70] Until similar work is done for MAAs, this paper might stimulate the classification process, making comparisons between studies more standardized.

To date, there is not *one* meta-analysis on this disease, and the explanation is part the rarity of the disease, and part that the reporting is too disparate making comprehensible meta-analysis impossible. The purpose of presenting a suggestion for reporting items is to facilitate comparisons between studies in the future.

However, a consensus document to settle these issues is warranted. Such document would desirably also contain reporting standards, as the ones proposed in this article were a mere synthesis of obvious divergent reporting, or lack thereof in the literature. Until then, the diagnostic syndromic algorithms used by the teams in Taipei, Taiwan, and Uppsala, Sweden, will have to suffice, where a combination of clinical, laboratory and imaging findings compose the basis for the diagnostic workup.[8,29]

Conclusions

This article puts an emphasis on the need to standardize definition, terminology, and diagnostic criteria for MAAs and proposes reporting items enhancing comparability between studies.

Author Contributions

Conception and design: KS, PGdS; Analysis and interpretation: KS, PGdS; Data collection: KS; Writing the article: KS,

PGdS; Critical revision of the article: KS, PGdS; Final approval of the article: KS, PGdS; Overall responsibility: KS.

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