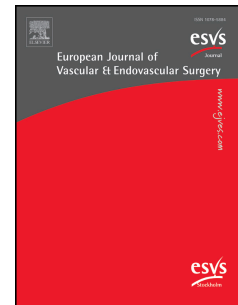# Journal Pre-proof

Infective Native Aortic Aneurysms: A Delphi Consensus Document on Terminology, Definition, Classification, Diagnosis, and Reporting Standards

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Infective Native Aortic Aneurysms: A Delphi Consensus Document on Terminology, Definition, Classification, Diagnosis, and Reporting Standards

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on behalf of the academic research consortium of infective native aortic aneurysm (ARC of INAA).

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What does this study/review add to the existing literature and how will it influence future clinical practice

This Delphi study established the first consensus document on infective native aortic aneurysm regarding terminology, definition, classification, diagnostic criteria and algorithm, as well as reporting standards. The results of this study create essential conditions for future scientific research on this disease.

ABSTRACT

Background: There was no consensus regarding the terminology, definition, classification, diagnostic criteria and algorithm, nor reporting standards for the disease infective native aortic aneurysm (INAA), previously known as mycotic aneurysm. The aim of this study was to establish this by performing a consensus study.

Methods: The Delphi methodology was used. The two principal investigators (PI), invited 37 international experts via mail. Four Delphi rounds were performed, two weeks each, using an online questionnaire, initially with 22 statements and 9 reporting items. The panelists rated the statements on a five-point Likert scale. Comments on statements were analysed, statements revised, and results presented in the iterative rounds. Consensus was defined as

≥75% of the panel rating a statement strongly agree or agree on the Likert scale, and consensus on the final assessment was defined as Cronbach's alpha coefficient > .80.

Results: All 38 panelists fulfilled all four rounds, resulting in 100 % participation and agreement that this study was necessary, and the term INAA was agreed to be the most optimal. Three more statements were added based on the results and comments of the panel, resulting in a final 25 statements and 9 reporting items. All 25 statements reached an agreement of ≥87%, and all 9 reporting items reached an agreement of 100%. The Cronbach's alpha increased for each consecutive round; round 1 = .84, round 2 = .87, round 3 = .90, and round 4 = .92. Thus, consensus was reached for all statements and reporting items.

Conclusion: This Delphi study established the first consensus document on infective native aortic aneurysm regarding terminology, definition, classification, diagnostic criteria and algorithm, as well as reporting standards. The results of this study create essential conditions for scientific research on this disease. The presented consensus will need future amendments in accordance with newly acquired knowledge.

Key Words: infective aneurysm, Delphi study, mycotic aneurysm, definition, diagnosis, criteria, classification

INTRODUCTION

In 1885, Sir William Osler presented a case of a man with infective endocarditis and its association with four concomitant aortic aneurysms with morphological fungal resemblance.(1) The term *mycotic* was introduced to describe these aneurysms. Later, when it was understood that most of these aortic aneurysms were caused by bacterial infection, it became evident that the term *mycotic,* implicating a fungal genesis, was a misnomer.(2)

The term mycotic has since been criticized, while a plethora of poorly defined terms have been in use over the years.(3) The disease itself is rare, making it difficult to study and statistical analyses challenging, meanwhile its management is very demanding and the condition carries a high mortality, a nadir of vascular surgery.(4, 5) Still, to this day, there is no consensus regarding terminology, definition, classification nor diagnostic criteria for this pathology.(6, 7)

Two recently published systematic literature reviews have demonstrated that this lack of standardisation results in divergent reporting and great difficulties in comparing studies.(4, 8) This problem severely hampers development of scientific knowledge of this disease. Due to current various terminology and disparate definitions, and sometimes non-existant diagnostic work-ups in publications, consensus on these issues as well as reporting standards is warranted to facilitate study comparability. (4, 8-12)

A new, clearly defined term was introduced for this disease in 2020 - *infective native aortic aneurysm* (INAA).(6) The word infective was chosen in analogy with infective endocarditis, and the word native to explicitly exclude other infectious diseases of the aorta, such as aortic vascular graft and endograft infections (VGEI) and secondary aortic fistulas.(13) Along with the new term, propositions for definition, classification, diagnostic criteria, and reporting standards were made.

The aim of this study was to form an academic research consortium (ARC) for the disease entity infective native aortic aneurysm, in order to establish Delphi consensus on terminology, definition, classification, diagnostic criteria and algorithm, as well as reporting standards. This could create the essential conditions for scientific advancement in all regards of the disease.

MATERIALS AND METHODS

The study was performed using an online survey tool (www.surveymonkey.com) from January 2022 until April 2022. A modified Delphi(14-17) approach was used to reach consensus based on the components of the editorial *Infective Native Aortic Aneurysms: Call for Consensus on Definition, Terminology, Diagnostic Criteria, and Reporting Standards* published in 2020 in the European Journal of Vascular and Endovascular Surgery.(6)

The Delphi panelists could comment and rate each statement using a five-point Likert scale: 1 = strongly agree, 2 = agree, 3 = neutral, 4 = disagree, or 5 = strongly disagree. Consensus was *a priori* defined if ≥75% of the panelists agreed (1-2) or disagreed (4-5) on the Likert scale. This was applied to proposed statements regarding terminology, definition, classification, diagnostic criteria and diagnostic algorithm. On reporting items, the Likert scale was not used. Instead, panelists could vote Yes or No and also had the possibility to comment on the items. Consensus was *a priori* defined for the reporting items if ≥75 % of the panelists chose the same answer. The facilitators of the study were authors KS and TRW, who were allowed to vote, but not comment on the statements.

Development of the survey

The principal investigators were KS and TRW. Ethical approval was not necessary, since the study is not dealing with patient data or biological material.

The aforementioned editorial was a distillate from four systematic literature reviews published between 2018-2021 covering the subjects of terminology, definition, classification, diagnostic criteria, treatment management, procurement of microbiological specimens, and the role of 18F-FDG-PET-CT.(3, 4, 18, 19) The content of the editorial was for this study supplemented by additional information regarding the importance and the methods of microbiological specimen collection, interpretation of microbiological findings, and the role of computed tomography and 18F-FDG-PET-CT.

Data from all the reviews, and the respective additionally included studies, was summarized by KS, subsequently controlled and approved by TRW. See **Figure 1** for the literature review process, and development of the survey.

Developing the academic research consortium and Delphi panel recruitment

The academic research consortium of INAA (ARC of INAA), consisting of international experts in the field who agreed to participate in the panel, formed the Delphi panel.
An expert was defined as an active researcher on the disease INAA, who had extensive practical knowledge of its management, or who was part of a writing group of international guidelines related to the disease. The experts were invited by e-mail including the study protocol outlining the aim of the study, the aforementioned editorial, and information of formation of the ARC of INAA.(6)
Purposive sampling was used to ensure wide international representation. Although consensus on the sample size of a Delphi panel is absent, there is a general recommendation to have15-30 participants.(14-17) Therefore, 39 experts from 17 countries were invited to participate in

the current study.

Membership of the Delphi panel was kept confidential throughout the study.(14-16) Experts who accepted the invitation to the ARC and the study, and fulfilled all the Delphi rounds constituted the panelists of the study and were offered co-authorship. Experts not actively participating in the Delphi process would be excluded from further rounds. Their contribution until the time of exclusion would be included in the analysis and they would be acknowledged for this in the final manuscript.

Executing the Delphi study

Round 1: Panelists voted on all statements and reporting items in an online questionnaire. Panelists also had the possibility to anonymously comment on each statement.

Rounds 2-4: The voting results, comments on statements and reporting items were then analyzed by the principal investigators. This information was then provided to the panelists by an anonymized summary of the results before commencing the following round. The statements voted upon could be revised during the course of the study, as a response to the results of the previous round. Each panelist's vote or comment was given equal weight. Panelists were encouraged to re-vote and comment on all statements in the online questionnaire. New statements and reporting items, or revisions of the statements and items proposed by the panelists were marked in the subsequent round for clarity, transparency, and uniformity.

All rounds were stopped once all panelists had replied, or after a maximum of three weeks. The Delphi process was planned for four rounds.

Statistics

The Cronbach's alpha coefficient was used to determine the internal consistency of the assessment tool after each round. The Cronbach's alpha value demonstrates how closely related a set of test items are as a group, and varies between 0 -1, with 1 corresponding to 100% consistency. Consensus on the final round 4 was defined as Cronbach's alpha > .80. Categorical variables were expressed as proportions (%). SPSS 25.0 (IBM, Armonk, NY, USA) was used for statistical analysis.

RESULTS

Out of 39 identified and invited experts, 38 agreed to participate, and thus formed the panelists of the Delphi study. The one who declined did so because of doubts of competence in the subject of the study. All panelists were physicians, specialized in the following: vascular surgery n = 32 (84.2 %), radiology n = 3 (7.9 %), cardiothoracic surgery n = 1 (2.6 %), cardiovascular surgery n = 1 (2.6 %), plastic and reconstructive surgery n = 1 (2.6 %). The geographical distribution of the panelists was: Europe n = 27 (71.1 %), Asia n = 7 (18.4 %), and North America n = 4 (10.5 %).

Figure 1 demonstrates the development of the survey, invitation of panelists, and consecutive rounds with addition of statements.

Results of the survey

All 38 panelists fulfilled all four rounds within the given timeframe, resulting in 100% participation.

Delphi round 1 consisted of 22 statements on the rationale for conducting the study, followed by establishing statements on terminology, definition, classification, diagnostic criteria and

diagnostic algorithm, as well as 9 reporting items. Round 1 resulted in consensus (at least 75% agree or strongly agree) for all but one statement, the latter, which concerned procurement of microbiological specimens for culture other than the aorta and blood.

Delphi round 2 was amended according to the comments of the panelists by adding two statements on procurement of microbiological specimens (# 15 and # 18), and how the results should be interpreted, and revision of the statement in round 1 which did not reach consensus. Round 2 resulted in consensus on all 24 statements and 9 reporting items.

Delphi round 3 included one more statement than the previous, based on the panelists' comments on the use and role of 18F-FDG-PET-CT in diagnosing INAA. Round 3 resulted in consensus on all 25 statements and 9 reporting items.

The final Delphi round 4 consisted of 25 statements and 9 reporting items, and consensus was reached for all. For details see flowchart in Figure 1.

The Cronbach's alpha increased with each consecutive round: round 1 = .84, round 2 = .87, round 3 = .90, and round 4 = .92.

The final established statements and the final reporting standards, with respective levels of agreement, are listed in Table 1 and Table 2 respectively.

DISCUSSION

This is the first consensus document on the disease infective native aortic aneurysm. By standardizing terminology, definition, classification, diagnostic criteria, diagnostic algorithm, and reporting standards this study creates essential conditions for scientific advancements regarding the disease. The possibility for inter-study comparability and meta-analyses should now increase, which is very important since gathering and evaluating large numbers of patients is very demanding due to the rarity of the disease. In the only two existing systematic

literature reviews on the treatment of INAA, there were issues on inherent uncertainties regarding which studies were eligible and non-eligible, which highly influenced the results and conclusions of the respective studies.(4, 8, 12) The present study could potentially be seminal in this regard.

The study is the result of 100% participation of all experts (no dropouts over all four rounds) generating a high level of agreement throughout the entire content of the study. The Cronbach's alpha values indicate high internal consistency of the survey, which increased with each round. The iterative manner, the anonymity of the panelists, the ability to comment and read others' comments, and to reconsider every vote in each round strengthens honest and well-reflected answers. The additional sense of a consensus document is to equalize the impact of views of dominant panel members, and hence allow for an even group dynamic where all participants play an equal role.(20)

There was 100% agreement that this study was necessary. There was 95% agreement of the definition, 92% agreement that *mycotic* is an imprecise historical misnomer, and there was 87% agreement that a more appropriate term would be *infective native aortic aneurysm*. This emphasizes the value and importance of introducing a new term for this disease, which is both more correct and also not historically associated with previous ill-definitions or misconceptions of the disease, that do not align with this document. Arguably, the ideal term would be *infective aortic aneurysm*, more simple and easy on the tongue, but as many publications still mix INAA with aortic VGEI or aortic fistulas, the word *native* is pertinent to explicitly distinguish these disease entities from one another. The definition of INAA, statements 5 - 9, also emphasizes the exclusion of aortic VGEI and aortic fistulas. However, it must also be acknowledged that both aortic VGEI and aortic fistulation, may respectively develop as a complication to treatment of INAA or a consequence of the disease.

The classification of INAA resulted in a 95% agreement. This could be important for future epidemiological work.

In total, 10 (40%) statements resulted in 100% agreement, including the essential preoperative diagnostic work-up, which should consist of a combination of clinical evaluation, laboratory results, and imaging findings. It is key to observe that a positive culture is not a requisite to make the diagnosis, and that the recommended first line imaging modality is contrast enhanced computed tomography. Without a pathognomonic symptom, laboratory test or radiological sign, the definite diagnosis will sometimes remain challenging, however consensus on this is indispensable.

With 87% agreement, it was decided that 18F-FDG-PET-CT might be helpful in making the diagnosis of INAA. Further, with 95% agreement it was acknowledged that the role of 18F-FDG-PET-CT in making the diagnosis of INAA is not clear, but in the case of 2/3 clinical criteria (classified as probable INAA) there is a potential role and value of performing a 18F-FDG-PET-CT. This implicit statement is the result of a lack of studies in the field, which hopefully will be resolved in the near future.(16)

All nine reporting items resulted in 100% agreement. However, in reporting item number nine, on reporting survival outcome including confidence interval, it should be added that hazard ratios should also preferably be reported to enhance the possibility for performing meta-analyses, even though median survival rates may also be used in time-to-event analyses. Also, in reporting item number nine, on reporting infection-related complications, it would be desirable to report the separate outcomes individually, since sepsis, aortic VGEI, recurrent infective aortic aneurysm, and aortic fistulas, do not have an inter-comparable impact on patient survival.

Limitations

To achieve consensus the Delphi methodology has become accepted, however there is no gold standard for which level of agreement consensus is needed.(20) In this study, the level of 75% agreement was the used, which was the median threshold to define consensus in a recent systematic literature review on the subject.(16) The panel size is generally recommended to consist of at least 12 experts on the field of interest, and panel sizes of more than 30 have been shown to add little to the results, and being difficult to maintain following low response rates. To invite non-experts is not recommended. This study contained 38 panelists, because the invitation acceptance rate was very high. Selecting the appropriate panelists is probably one of the most important steps in the methodology, since it directly relates to the quality of the study results. A significant criticism to this study must be highlighted that no infectious disease specialists participated. This was due to inability in finding specialists who fulfilled the expert criteria. This will have to be resolved for an eventual upcoming consensus study on management and treatment of INAA. There was broad representation from Europe, North America, and Asia. However, a possible limitation was not to have experts from other continents. Inter-specialty and inter-origin differences were not analysed.

Another limitation of the study was to omit to define *recurrent infective aortic aneurysm*; patients who are treated for an INAA and postoperatively develop a new infective aortic aneurysm. Even though this is a rare complication, it does occur, and might pose specific challenges. Unaddressed, was also whether the diagnostic algorithm developed in this study also could be applied to peripheral infective native aneurysms. While awaiting consensus for that, using this algorithm seems appropriate. A statement on etiology including ruling out infective endocarditis, and presence of psoas abscess would have been desired, and is recommended for reporting on this disease.

CONCLUSION

This Delphi study managed to establish the first consensus document on the disease of infective native aortic aneurysm regarding terminology, definition, classification, diagnostic criteria and algorithm as well as reporting standards. The results create essential conditions for scientific research of this disease. The presented consensus will need future amendments in accordance with newly acquired knowledge.

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Table 1: The final consensus statements, the results from Delphi round #4.

Statements	Consensus in round #4
#1 - There is a lack of consensus in the literature regarding terminology, definition, classification, diagnostic criteria, and reporting standards of aortic aneurysms arising due to infection, more commonly known as mycotic or infected aortic aneurysms.	100 %
#2 - International consensus amongst experts on terminology, definition, classification, diagnostic criteria, and reporting standards for aortic aneurysms due to infection would improve and facilitate standardized research in this field.	100 %
#3 - The term mycotic aortic aneurysm is a historical misnomer and is imprecise whilst implicating a fungal genesis.	92 %
#4 - A more appropriate term would be infective native aortic aneurysm (INAA) in analogy with infective endocarditis. This to explicitly replace mycotic by infective, and native to exclude aneurysms arising in an aorta, which has previously undergone surgery.	87 %
#5 - The definition of INAA is an aortic aneurysm, which is caused by microbial infection of the aortic wall. The infection causes degradation of the vessel wall, resulting in formation of a localized aneurysm.	95 %
#6 - The microbial infection is predominantly bacterial, but may also be fungal, or possibly viral in patients with advanced HIV-infection.	95 %
#7 - An aorta with extensive atherosclerosis, or a preexisting aneurysm, is more susceptible to such infection.	95 %
#8 - The common definition of degenerative aortic aneurysm based on diameter is not applicable to INAA because the morphology is predominantly saccular, multilobular, amorphous but could also be fusiform.	95 %
#9 - Other infective states involving the aorta, such as aortic vascular graft/endograft infections and secondary aorto-enteric or -bronchial fistulas, are not part of this disease entity.	100 %
#10 - Classification of various INAA should preferably be done according to the following modification of the previously published subgroups based on pathophysiology[5]: A) Blood-borne bacteria inoculated in the aortic wall during bacteremia. B) Infection of pre-existing aneurysm due to blood-borne bacteria. C) Due to septic emboli lodging in the aortic wall from infective endocarditis. D) Direct spread of infection from adjacent infected tissue.	95 %

E) Aneurysms developing in patients with advanced HIV-infection.	
F) Unknown.	
#11 - Patients with INAA are typically symptomatic. The two most common symptoms are pain and fever. Other infection related symptoms might be present such as fatigue or malaise, or local symptoms depending on the anatomical location of the aneurysm. Patients may have a concomitant infection, and may express specific symptoms from that.	100 %
#12 - Patients suffering from INAA typically show elevated inflammatory markers such as C-reactive protein and leukocytes.	100 %
#13 - Cultures refer to any culture harvested during the period of illness. Even though a positive culture result is not a requisite for making the diagnosis of INAA, procurement of microbiological specimens is absolutely fundamental and should be of highest priority.	100 %
#14 - Cultures should ideally be harvested before initiation of any antimicrobial therapy.	100 %
#15 - Micro-organism identification should be performed in a similar approach to that of infective endocarditis; to use at least three blood cultures (both aerobic and anaerobic) from different venopuncture sites, and to repeat blood cultures every 24 to 48 hours until bloodstream infection has cleared in order to certify effectiveness of treatment, and to use PCR when agar cultures are negative.	95 %
#16 - Micro-organism identification from the aneurysm wall should be obtained when possible.	95 %
#17 - Positive cultures from the aneurysm, aneurysm adjacent tissue or blood will be considered more likely to identify the causative agents than other positive results from other locations.	97 %
#18 - Procurement of specimens for culture from urine and the respiratory tract or other symptomatic organs should also be performed in order to capture possible causative specimens.	100 %
#19 - The recommended first line imaging modality for making the diagnosis of INAA is contrast enhanced computed tomography.	100 %
#20 - Findings on computed tomography typical for INAA are: rapid expansion of aneurysm, saccular aneurysm, multi-lobular aneurysm or eccentric aneurysm, periaortic soft tissue mass/gas/fluid, and an atherosclerotic aorta. There might also be multiple aneurysms along the aorta.	92 %
#21 - The preoperative diagnostic work-up should consist of a combination of the following three clinical criteria: 1) Clinical presentation: either pain, fever ≥38° C, sepsis and/or concomitant infection. 2) Laboratory results: either elevated inflammatory markers like C-reactive protein and leukocytes, and/or positive cultures*.	100 %

3) Imaging: either rapid expansion of aneurysm, saccular aneurysm, multi-lobular aneurysms/eccentric aneurysms, periaortic gas/soft tissue mass/fluid, and multiple aortic aneurysms with the aforementioned characteristics.

Cultures refer to any culture harvested during the period of illness. Even though a positive culture result is not a requisite for making the diagnosis of INAA, procurement of microbiological specimens is absolutely fundamental and should be of highest priority.

#22 - The diagnostic algorithm for INAA is: Clinical criteria Definite diagnosis: 3/3 clinical criteria and no differential diagnosis being more likely. Probable diagnosis: 2/3 clinical criteria and no differential diagnosis being more likely. Not probable diagnosis: 1/3 clinical criteria. *OR* Pathological criteria Intra-operative finding of pus/abscess in the aneurysm wall, or positive microbiological culture or histology from guided aspiration from aneurysms with clinical suspicion of INAA (definite or probable INAA).	92 %
#23 - If available and the patient's status permits, 18F-FDG-PET-CT may be helpful in making the diagnosis of INAA.	87 %
#24 - The role of 18F-FDG-PET-CT in making the diagnosis of INAA is not clear. In the case of two out of three clinical criteria (classified as probable INAA) there is a potential role and value of performing a 18F-FDG-PET/CT. Specific SUV_{max} cut-off values to make the diagnosis of INAA are lacking.	95 %
#25 - Infection-related complications (IRC) is a composite of postoperative infectious complications consisting of either persistent or recurrent sepsis, development of vascular graft or endograft infection, recurrent infective aortic aneurysm, or development of aorto-enteric or -bronchial fistula.	95 %

Table 2: The final reporting standards, the result of the nine reporting items with the respective level of consensus from round #4.

Reporting items to be included in research on INAA to enhance comparability between studies, and make meta-analyses possible are:	Consensus in round #4
- Use of the above (see Table 1) accounted terminology, definition, classification, and diagnostic criteria.	100 %
- Criteria of exclusion: e.g. aortic vascular graft and endograft infections, secondary aorto-enteric or -bronchial fistulas, inflammatory aneurysms, penetrating aortic ulcers etc.	100 %
- Patient characteristics: medical history, e.g. cardiopulmonary disease, smoking, immunosuppressive state/medication; data on presentation: symptoms, concurrent or recent infection.	100 %
- Laboratory results: levels of inflammatory markers such as C-reactive protein and leukocytes, microbiological cultures, results of polymerase chain reaction.	100 %
- Imaging findings: aneurysm morphology such as fusiform, saccular, eccentric, multilobular; rapid expansion, peri-aortic gas / soft tissue mass / fluid; imaging modality (computed tomography, magnetic resonance imaging, positron emission tomography). Rupture.	100 %
- Aneurysm anatomy: level of aorta engaged.	100 %
- Details on surgical treatment: open repair; location of aortic clamp; in situ reconstruction or extra-anatomic bypass and graft material; endovascular aortic repair; type of stent graft, hybrid procedure. Include non-operated patients.	100 %
- Details on antimicrobial treatment: preoperative and postoperative duration and drugs.	100 %
- Outcome and follow-up: duration, symptoms, laboratory results, imaging modality and results, survival with confidence interval, bacteriology in case of infection-related complications, need for reoperations.	100 %

Figure 1. Flowchart of the development of the survey, and the following Delphi rounds