Infective Native Aortic Aneurysm

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Infective Native Aortic Aneurysm: a Delphi Consensus Document on Treatment, Follow Up, and Definition of Cure

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WHAT THIS PAPER ADDS

This Delphi study established a consensus document on infective native aortic aneurysm regarding overall management, surgical and antimicrobial treatment, follow up routines, duration of antimicrobial treatment, and definition of disease cure. This document was established to support clinicians and researchers dealing with this rare disease, where evidence is lacking, to guide management as a detailed supplement to current guidelines.

Objective: Evidence is lacking to guide the management of infective native aortic aneurysm (INAA). The aim of this study was to establish expert consensus on surgical and antimicrobial treatment and follow up, and to define when an INAA is considered cured.

Methods: Delphi methodology was used. The principal investigators invited 47 international experts (specialists in infectious diseases, radiology, nuclear medicine, and vascular and cardiothoracic surgery) via email. Four Delphi rounds were performed, three weeks each, using an online questionnaire with initially 28 statements. The panellists rated the statements on a five point Likert scale. Comments on statements were analysed, statements were revised and added or deleted, and the results were presented in the iterative rounds. Consensus was defined as $\geq$ 75% of the panel rating a statement as strongly agree or agree on the Likert scale, and consensus on the final assessment was defined as Cronbach's alpha $>$ 0.80.

Results: All 49 panellists completed all four rounds, resulting in 100% participation. One statement was added based on the results and comments of the panel, resulting in 29 final statements: three on need for consensus, 20 on treatment, five on follow up, and one on definition of cure. All 29 statements reached agreement of $\geq$ 86%. Cronbach's alpha increased for each consecutive round; round 1, 0.85; round 2, 0.90; round 3, 0.91; and round 4, 0.94. Thus, consensus was reached for all statements.

Conclusion: INAAs are rare, and high level evidence to guide optimal management is lacking. This consensus document was established with the aim of helping clinicians manage these challenging patients, as a supplement to current guidelines. The presented consensus will need future amendments in accordance with newly acquired knowledge.

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INTRODUCTION

Infective native aortic aneurysm (INAA) is an acute disease associated with a high mortality rate (up to 100% without surgery) and is possibly the most challenging disease within the fields of vascular, cardiovascular, and cardiothoracic surgery. Treatment of INAA comprises both antimicrobial treatment and surgery.[1–4] However, no randomised controlled studies or larger prospective studies exist to guide management. Current knowledge on treatment of

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this disease relies on a few retrospective population based studies, systematic literature reviews, and larger retrospective studies.[3–14] Most of these studies report survival after treatment, some also report on the development of infection related complications (IRCs), but none define or evaluate when a patient with INAA might be considered cured.[13] The latter would be pertinent as an additional study endpoint as well as helping decide when antimicrobial medications can be safely stopped and follow up routines decreased or possibly ended.

The guidelines of three medical societies address the management of INAA, namely the American Heart Association (AHA), the European Society for Vascular Surgery (ESVS), and the Japanese Circulation Society (JCS).[15–17] In the current versions, these guidelines are not dedicated to INAA but only include brief chapters, which do not elaborate on its management in detail and omit follow up. This might be due to the rarity of the disease, lack of evidence on treatment, or due to difficulty in interpreting the disparate findings on treatment in the literature.

In 2022, the INAA Academic Research Consortium (ARC) was formed with the aim of gathering global expertise on the disease and establishing consensus on basic scientific needs to advance in the field; definition, terminology, classification, diagnostic criteria, and reporting standards. In 2023 the results were published, forming a cornerstone for future research.[18]

The aim of this study was to establish expert consensus regarding medical and surgical treatment of INAA, follow up strategy including clinical, laboratory, and radiological examinations, and to define when INAA might be considered cured. The rationale for this is to fill in knowledge gaps and to aid clinicians manage patients with this disease, where evidence is lacking, and guidelines are incomplete.

MATERIALS AND METHODS

This study was performed using an online survey tool (https://www.surveymonkey.com) from April – July 2023. A modified Delphi approach[19–23] was used to reach consensus on the optimal management of INAA including: context and need for consensus; the use of multidisciplinary team (MDT) conferences; surgical approaches and timing of surgery; antibiotic treatment (antimicrobial coverage, duration, consideration of antimicrobial resistance); follow up (clinical, laboratory, and radiological examinations and timing, the role of nuclear imaging); as well as defining cure.

The Delphi panellists rated each statement using a five point Likert scale: 1 = strongly agree; 2 = agree; 3 = neutral; 4 = disagree; and 5 = strongly disagree. In addition, panellists could also add comments for each statement.

Consensus was *a priori* defined if $\geq$ 75% of the panellists agreed (1 – 2) or disagreed (4 – 5) on the Likert scale.[21] This was applied to all proposed statements.

The principal investigators and facilitators of the study (K.S. and T.R.W.) were allowed to vote but not to comment on the statements. A third author (M.G.) did not vote but assessed the comments and votes of the panellists.

Development of the survey

Since the study did not deal with patient data or biological material, ethical approval was not necessary.

Guidelines on INAA, nationwide population based cohorts, systematic literature reviews, and larger case series were scrutinised in order to create a basis for statements that reflect and summarise best evidence or practice on surgical and antimicrobial treatment and follow up, and areas where lack of evidence and guidelines exist to try filling these gaps with expert opinion. Specifically, the studies were scrutinised on overall management, the role and use of MDTs, surgical approach and outcome (open surgical repair [OSR], endovascular aneurysm repair [EVAR], as well as the use of different conduit materials), timing of surgery, management of fistulation, risk of post-operative IRCs, microbiology, antibiotic therapy management (pre-operative therapy and duration, post-operative duration), follow up (clinical examination, laboratory results, imaging routines, the role and use of nuclear imaging techniques), cessation of antibiotic therapy, and definition of cure.

T.R.W., M.G., and K.S. drafted propositions for statements. This served as the basis for the first round, which consisted of 28 statements. As detailed further below, statements were then refined during the subsequent Delphi rounds according to expert comments (Fig. 1).[24]

The Academic Research Consortium and Delphi panel recruitment

Development of the ARC of INAA has been described previously.[18] An expert was defined as an active INAA researcher who has extensive practical knowledge of its management, or who was part of a writing group of international guidelines related to the disease. To address antimicrobial treatment as well as to identify the role of nuclear medicine imaging, specialists in infectious diseases and nuclear medicine physicians were recruited. The aim was for broad international representation. Experts were invited by email including the study protocol outlining the aim of the study as well as information on the ARC of INAA. Membership of the Delphi panel was kept confidential throughout the study. Experts not actively participating in the Delphi process were excluded from further rounds.

Executing the Delphi study

Round 1: Panellists voted on all statements and had the option to comment anonymously.

Rounds 2 – 4: The voting results and comments were then analysed by the investigators. This information was provided to the panellists by an anonymised summary of the results before commencing the following round. The statements voted upon could be revised, added to or deleted by the investigators during the course of the study. Each panellist's vote or comment was given equal weight. New statements and revisions of the statements proposed

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by the panellists were labelled in the subsequent round for transparency.

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

Statistics

Categorical variables were expressed as percentages. Cronbach's alpha coefficient was used to determine the internal consistency of the assessment tool after each round. Cronbach's alpha varies between 0 — 1, with 1 corresponding to 100% consistency, and demonstrates how closely related a set of test items is as a group. Consensus in the final round 4 was defined as Cronbach's alpha $>$ 0.80.[25] IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

RESULTS

Of 51 identified experts, 49 agreed to participate (including K.S. and T.R.W.), and these formed the panellists of the Delphi study. All panellists were physicians, with the following subspecialties: vascular surgery, 33 (67%); cardiovascular and cardiothoracic surgery, three (6%); infectious diseases, six (12%); nuclear medicine, five (10%); and radiology, two (4%). The geographic distribution of the panellists was as follows: Europe, 40 (82%); Asia, five (10%); North America, three (6%); and Oceania, one (2%).

All panellists completed the four rounds within the given timeframe, resulting in 100% participation.

Delphi round 1 consisted of 28 statements on the rationale for conducting the study, followed by statements on surgical treatment and timing, pre- and post-operative antibiotic treatment and duration, follow up, and finally a definition of cure. Round 1 resulted in consensus ($\geq$ 75% agree or strongly agree) for 22 statements (79%).

Delphi round 2 was amended according to the comments of the panellists by adding one statement on post-operative antibiotic duration (#21) as well as revision of the statements in round 1 that did not reach consensus. Round 2 resulted in consensus on all 29 statements. Further minor wording revisions were performed according to expert opinion in the comment field.

Delphi round 3 continued with consensus on all 29 statements. Further minor wording revisions were performed according to expert opinion in the comment field.

Delphi round 4 consisted of 29 statements, and consensus was reached for all. For details, see the flowchart in Figure 1.

Cronbach's alpha increased with each consecutive round: round 1, 0.85; round 2, 0.90; round 3, 0.91; and round 4, 0.94. Table 1 shows the final version of the established statements with respective levels of agreement in round 4.

DISCUSSION

The first consensus document from the ARC of INAA focused on establishing consensus on basic scientific standardisation (definition, terminology, classification, diagnostic criteria, and reporting standards) in order to create a common perception of the disease as well as to facilitate and homogenise research on the disease.[18] This second consensus study is the consecutive step, addressing overall management and detailing surgical management, antimicrobial therapy, follow up routines and requirements, the role of nuclear medicine imaging, and cessation of antimicrobial therapy, as well as offering a definition of cure of the disease.

With a participation rate of 100% and consensus for all statements, the final statements mirror the opinion of an international interdisciplinary group of 49 independent experts (aortic surgeons, infectious disease specialists, nuclear medicine specialists, and radiologists). Furthermore, Cronbach's alpha confirmed high internal consistency of the survey and increased for each consecutive round.

In concise terms, the study concluded that individuals diagnosed with INAA should receive care overseen by a MDT, and the surgical approach should be tailored to the specific patient with consideration given both to OSR and EVAR as viable options. Administration of antibiotics should also be personalised and guided by specialists in infectious diseases, both in the short and long term. Vigilant post-treatment monitoring is imperative for timely detection of IRCs. Additionally, the document provides a clear criterion for when the disease could be considered cured.

There was consensus that this study was necessary. The three first statements arguing the need for expert consensus on surgical and antimicrobial therapy, follow up, and definition of cure showed an agreement of 96%, 96%, and 94%, respectively. There was 98% agreement that INAA patients should be managed by a MDT approach and that patients should preferably be treated in specialised centres (#4). The AHA guidelines recommend MDT management (Class I, Level C) but do not mention management at specialised centres.[17] The latest ESVS guidelines recommend both MDT management and for patients to be treated at specialised centres (Class I, Level C).[16] Due to the complexity of the disease this would be the most adequate management to ascertain optimal care. The JCS guidelines are a narrative on INAA and offer no specific recommendations.[15]

Curative and conservative INAA treatment was defined (#5, #6). Curative treatment warrants both antimicrobial and surgical treatment (OSR or EVAR). Surgical treatment is recommended irrespective of the size of the aneurysm owing to the high risk of rapid progression, aortic rupture, and death, which is in line with the ESVS guidelines (Class I, Level C recommendation),[16] and in the other guidelines this is not mentioned.

Conservative treatment was defined as antimicrobial treatment alone or in combination with percutaneous drainage. Until demonstrated otherwise, conservative treatment is regarded as palliative treatment and should be reserved for selected patients who are considered too frail for surgery or where surgery is not deemed feasible.[2] These distinctions between curative and conservative do not exist in any current guidelines.[15–17]

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Surgical management, detailed in statements #7 — #16, should be tailored to each patient, where both OSR and EVAR are options, and should be performed as soon as possible. The use of endovascular techniques offers a potentially fast and minimally invasive treatment option that may have an advantage over open repair in elderly and unfit patients, as well as in the setting of rupture where immediate repair is indicated. OSR is typically reserved for fit patients and consists of complete debridement of infected tissue, followed by *in situ* reconstruction and graft coverage with vital tissue (e.g., omental flap). With 90% agreement, there was consensus that the use of biological grafts (e.g., autologous vein, homograft, pericardial graft) probably reduces the risk of graft infection.[6,26–28] Extra-anatomic bypass was regarded as a second choice to *in situ* reconstruction because of the risk of aortic stump blowout. The ESVS guidelines implicitly state that surgical technique for INAA should be considered based on the individual patient and lesion characteristics (Class IIa, Level C),[16] whilst the AHA guidelines published in 2016 recommend *in situ* reconstruction and regard EVAR as a bridge to open surgery (Class IIb, Level C).[17]

Focused research is needed to estimate the risk of IRCs after treating INAAs with or without debriding and excising the infected segment of the aorta, whether by OSR or EVAR, and the role of the remaining infected tissue after endovascular treatment needs to be explored.

Antimicrobial therapy is detailed in statements #17 — #23, with its timing, choice of drugs in the acute phase, and duration after surgery. Statement #27 details how to consider cessation of antimicrobial treatment. This section on antimicrobial therapy has not been elaborated in guidelines before. The choice of antibiotics, possible need to change drugs, need for combination treatment, possible biofilm development, local microbial resistance pattern, duration, and intolerance or allergy necessitates the involvement of infectious diseases specialists from the start and throughout treatment. Most scientific INAA reports have been published by surgeons and as a consequence information on bacteriology and antibiotic treatment have been neglected and are therefore lacking. Integration of infectious diseases specialists in the expert panel was vital. With limited scientific evidence for the antimicrobial regimens proposed in this study, all these statements would need further validation, preferably in randomised controlled studies, but due to the rarity of the disease observational studies are warranted. Similar to surgical procedures, antimicrobial therapy must be personalised, considering factors such as the patient's condition, the specific pathogen involved, the chosen surgical method, graft material, and the patient's response to treatment. The pre-operative antibiotic recommendations for unidentified pathogenic organisms were established due to the observation that approximately 80% of the pathogens associated with INAAs belong to *Streptococcus* spp., *Staphylococcus aureus*, *Salmonella* spp., and *Escherichia coli*, with some geographical variation.[4,7] Consensus was reached on recommending a minimum post-operative antimicrobial duration of six weeks after OSR with biological grafts, and 3 — 6 months after OSR using synthetic grafts and after EVAR. Lifelong antimicrobial therapy may be necessary in selected cases. The ESVS guidelines state that antibiotics against *S. aureus* and Gram negative rods should be commenced immediately after cultures, but do not offer specific drugs or treatment durations (Class I, Level C).[16] The AHA recommend a post-operative antibiotic treatment duration of six weeks to six months, without further detailing this statement (Class IIb, Level B).[17]

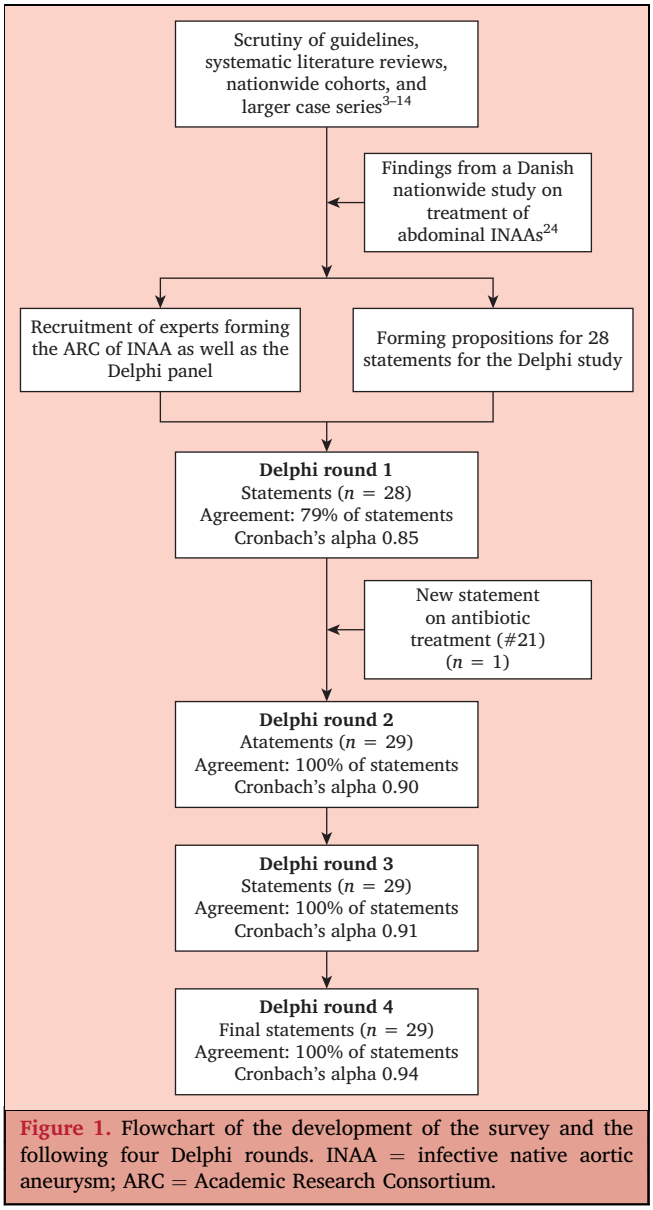

Figure 1. Flowchart of the development of the survey and the following four Delphi rounds. INAA = infective native aortic aneurysm; ARC = Academic Research Consortium.

Follow up is detailed in statements #24 — #28, including clinical, laboratory, and timing, and suggested computed tomography (CT) protocol. As with all aspects of patients with INAA, follow up also needs to be individualised. It has been demonstrated that 80 — 90% of IRCs (with an associated 50% mortality) develop during the first post-operative year, and particularly within the first six months, proving why this period is crucial for early detection of

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Table 1. Final statements and the respective level of consensus in Delphi round 4 on the management of infective native aortic aneurysm (INAA)

Statement		Consensus − %
#1	There is a lack of consensus on best surgical treatment of infective native aortic aneurysm (INAA). Consensus on surgical management could aid clinical practice and be of benefit for patients suffering from INAA.	96
#2	There is a lack of consensus on pre- and post-operative antimicrobial treatment (including duration) for patients with INAA. Recommendations on choice of antibiotics in the acute setting before identification of the microbiological pathogen as well as on duration after surgery could aid clinical practice.	96
#3	There is a lack of definition of when an INAA is considered cured. Establishing a definition of cure of INAA could aid clinical practice and research of INAA.	94
#4	Management of INAA should be performed in specialised centres with multidisciplinary expertise of cardiac and vascular surgeons, radiologists, infectious diseases specialists, and nuclear medicine specialists.	98
#5	Curative treatment of INAA consists of both surgical and antimicrobial treatment and is recommended irrespective of the size of the aneurysm owing to the high risk of rapid progression, aortic rupture, and death.	90
#6	Conservative INAA treatment is defined as antimicrobial treatment alone or in combination with percutaneous drainage. Until demonstrated otherwise, conservative treatment is not considered to be curative and should be reserved for selected cases as palliative treatment where surgery is not feasible.	88
#7	The choice of surgical treatment for INAA should be tailored to each individual patient, taking age, comorbidities, clinical status, and anatomical location of the aneurysm into account, coupled with the surgical expertise of the team.	92
#8	There is a lack of scientific evidence to prove the superiority of open surgical repair (regardless of graft material and approach) over endovascular aortic repair, and *vice versa*, when treating INAA.	86
#9	Endovascular INAA repair is a solution for patients where an adequate seal is possible to achieve. It may have an advantage over open repair in elderly and unfit patients, as well as in the setting of rupture where immediate repair is indicated.	90
#10	First choice of open surgical INAA repair consists of complete debridement of infected tissue, followed by *in situ* reconstruction and graft coverage with vital tissue (e.g., omental flap). Open repair is typically reserved for fit patients.	94
#11	It seems probable that the use of biological grafts (e.g., autologous vein, homograft, pericardial graft) reduces the risk of graft infection, but it has not been proven. The long term durability of biological grafts for INAA is unclear.	90
#12	Extra-anatomic bypass carries the risk of aortic stump blowout but might be an option in selected cases.	88
#13	Surgical treatment should be performed as soon as possible, and the exact timing depends on the clinical status of the patient.	94
#14	For severe pain, rupture or circulatory shock, immediate surgical treatment is indicated.	98
#15	For complicating fistulation to either the bowel or urinary tract, open surgical repair is required for curative treatment.	92
#16	The benefit of deferring surgical treatment to allow a certain period of pre-operative antimicrobial therapy to gain infection control and perhaps reduce infection related complications, is unclear, but carries a risk of rupture and therefore should be undertaken with caution.	96
#17	Antimicrobial treatment should be established according to infectious diseases specialists. Empirical intravenous antibiotic therapy should be initiated immediately after extensive sampling.	100
#18	For a *known* microbiological pathogen, directed antimicrobial therapy should be administered immediately intravenously.	98
#19	For an *unknown* bacterial pathogen, the initial antibiotic therapy administered should cover *Streptococcus* spp., *Staphylococcus aureus*, *Salmonella* spp. and *Escherichia coli*, since they constitute about 80% of culture positive pathogens of INAA globally. If immediate surgical treatment is indicated, the following antibiotics are possible options but should preferably be decided after consulting infectious diseases specialists: - cephalosporins (e.g., cefotaxime) with or without nitroimidazoles (e.g., metronidazole) or - cephalosporins (e.g., cefotaxime) with or without aminoglycosides (e.g., gentamicin) or - piperacillin/tazobactam or - carbapenems (e.g., meropenem)	96
#20	The local pattern of resistance has to be taken into consideration when choosing antimicrobial therapy: - In areas with a higher risk of MRSA, the addition of vancomycin should be considered. - In areas with a higher risk of resistance towards third generation cephalosporins (ESBL/AmpC), empirical treatment with piperacillin/tazobactam or meropenem should be considered. - The possibility of biofilm producing bacteria should be taken into consideration.	92

Continued

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Table 1-*continued*

Statement		Consensus − %
#21	The post-operative antibiotic duration should be tailored to each patient, taking surgical approach, microbiological specimen findings, local resistance pattern, response to treatment (clinically, laboratory, and imaging), and side effects into account.	96
#22	The minimum duration of antimicrobial therapy is six weeks. Such a short duration should only be considered after open surgical repair with biological grafts and according to infectious diseases specialists.	92
#23	After open surgical repair with synthetic grafts or after endovascular aortic repair, antimicrobial therapy should be continued for at least 3 − 6 months, and in selected cases, lifelong.	92
#24	Patients treated for INAA should be followed up closely after discharge, including clinical examination, laboratory tests (white blood cell count and C reactive protein), and imaging including contrast enhanced computed tomography (CT).	100
#25	Post-operative follow up with contrast enhanced CT should be used judiciously and individually. After all types of surgical treatment, contrast enhanced CT should be considered before hospital discharge to serve as baseline imaging. Suggested post-discharge imaging intervals are three, six, and 12 months, and yearly thereafter if the patient is asymptomatic and has normal laboratory tests (white blood cell count and C reactive protein).	92
#26	The role of ^{18}F-fluorodeoxyglucose positron emission tomography with CT (^{18}F-FDG PET/CT) and white blood cell scintigraphy with CT (WBCS CT) during follow up needs further research. In situations when CT is insufficient in visualising possible infection related complications the use of ^{18}F-FDG PET/CT and WBCS CT is indicated. (Infection related complications, e.g., sepsis, aortic vascular graft and endograft infection, development of aortic fistulation, recurrent infected aortic aneurysm). WBCS CT is preferred in the early post-operative phase and ^{18}F-FDG PET/CT starting from four months after surgery in order to be able to differentiate better between post-operative inflammation and infection.	94
#27	Before stopping antimicrobial therapy, the following minimum should be performed with no sign of continuous infection: clinical examination, laboratory tests (white cell blood count and C reactive protein), and imaging with contrast enhanced CT, followed by a multidisciplinary conference. In selected cases also ^{18}F-FDG PET/CT or WBSC CT could be considered. If signs of infection are present, antimicrobial therapy should be continued for at least another three months, followed by re-evaluation as above.	94
#28	Fever, fatigue, pain in the location of the graft or endograft, and or positive laboratory tests (white blood cell count and C reactive protein) should prompt high alertness for infection related complications, regardless of surgical approach.	100
#29	Cure of INAA is suggested to be defined as one year without antimicrobial therapy with no signs of persisting or recurrent infection on follow up, including clinical evaluation, laboratory tests, and imaging with contrast enhanced CT. (Rationale: 80 − 90% of infection related complications develop during the first 12 months after surgery.)	96

INAA = infective native aortic aneurysm; MRSA = methicillin resistant *Staphylococcus aureus*; ESBL = extended spectrum β lactamase; CT = computed tomography; ^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography with CT; WBCS CT = white blood cell scintigraphy with CT.

treatment failure.[4,13] The role of ^{18}F-fluorodeoxyglucose positron emission tomography with CT (^{18}F-FDG PET/CT) and white blood cell scintigraphy with single photon emission computed tomography with CT (WBCS SPECT/CT) is outlined, and these modalities are primarily recommended when CT is inconclusive.[29] The recent ESVS guidelines recommend an individualised post-operative antibiotic regimen and surveillance strategy based on patient factors, microbiology, and the surgical technique used (Class IIa, Level C).[16] The AHA do not offer recommendations on this.[17]

Suspicion of aortic vascular graft or endograft infection (VGEI) after INAA treatment should be evaluated according to the ESVS and European Association of Nuclear Medicine (EANM) guidelines for aortic VGEI.[29,30] Whenever a patient develops fever, fatigue, pain in the location of the graft or endograft, or shows positive laboratory tests (white blood cell count and C reactive protein) this should prompt high alertness for IRC, regardless of the type of surgical approach used. This situation is not mentioned in any current guideline.[15–17]

Definition of cure of INAA was established in the final statement #29: one year without antimicrobial therapy with no signs of persisting or recurrent infection on follow up including clinical evaluation, laboratory tests, and imaging with contrast enhanced CT. The introduction of this delineation as an additional study endpoint is imperative, as prior reports have focused solely on survival without addressing the attainment of a state of cure. This new parameter may prove instrumental in clinical decision making regarding the cessation of antimicrobial treatment, in conjunction with statement #27. Subsequent comprehensive investigations into the optimal duration of antimicrobial therapy hinge on the establishment of precise criteria for defining both cure and treatment failure, which involves the onset of IRCs. This definition of cure requires

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future validation. INAA cure is not yet mentioned in any guideline document.[15–17]

Limitations

The Delphi methodology has become an accepted approach to achieve expert consensus in clinical situations where evidence is difficult or challenging to gather.[19–23] The number of experts included in this study is in the upper limit of the recommendations. Nonetheless, it was considered vital to broaden the INAA ARC by including specialists in infectious diseases and nuclear medicine. One of the advantages with the Delphi methodology is that experts can vote and comment anonymously, and each vote and comment is weighted equally. This could have resulted in a problematic interpretation in some statements, e.g., statements on surgical treatment should intuitively be steered more by surgeons, and statements on antimicrobial treatment more by specialists in infectious diseases. However, this situation did not occur, perhaps thanks to constructive comments and explanations by the experts for the particular statements, which were subsequently reviewed by all panellists. Broad international representation was desired, but no experts from Africa or South America were included.

Future research includes validation of all these statements, hence supporting or rejecting them, and most will probably require revision with time. Large prospective, international registry studies are warranted as well as randomised controlled trials. Both would be difficult and arduous due to the rarity of the disease. To study rare diseases might require new research methodology to facilitate this, e.g., platform trials with stratified randomisation.[31]

Conclusion

INAA is rare, and high level evidence is lacking to guide optimal management. This consensus document was established with the aim of helping clinicians manage these challenging patients, as a supplement to current guidelines. The presented consensus will need future amendments in accordance with newly acquired knowledge.

CONFLICTS OF INTERESTS STATEMENT AND FUNDING

None.

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None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2023.12.008.

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