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Diagnosis of Aortic Graft Infection: A Case Definition by the Management of Aortic Graft Infection Collaboration (MAGIC)

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WHAT THIS PAPER ADDS

There is no universally accepted aortic graft infection case definition and clinical approaches to this complex condition differ widely with variable outcomes. Here, the Management of Aortic Graft Infection Collaboration (MAGIC), involving clinicians from several English hospital National Health Service Trusts with large vascular services, propose a formal case definition, derived by a process of multidisciplinary, expert consensus. The definition is readily applied in routine practice and aids early recognition. Importantly and towards development of evidence-based clinical guidelines that are presently lacking, it provides a consistent diagnostic standard, essential for clinical trial design and meaningful comparison between diagnostic and therapeutic strategies.

Objective/Background: The management of aortic graft infection (AGI) is highly complex and in the absence of a universally accepted case definition and evidence-based guidelines, clinical approaches and outcomes vary widely. The objective was to define precise criteria for diagnosing AGI.

Methods: A process of expert review and consensus, involving formal collaboration between vascular surgeons, infection specialists, and radiologists from several English National Health Service hospital Trusts with large vascular services (Management of Aortic Graft Infection Collaboration [MAGIC]), produced the definition.

Results: Diagnostic criteria from three categories were classified as *major* or *minor*. It is proposed that AGI should be suspected if a single *major* criterion or two or more *minor* criteria from different categories are present. AGI is diagnosed if there is one *major* plus any criterion (*major* or *minor*) from another category. (i) Clinical/surgical *major* criteria comprise intraoperative identification of pus around a graft and situations where direct communication between the prosthesis and a nonsterile site exists, including fistulae, exposed grafts in open wounds, and deployment of an endovascular stent-graft into an infected field (e.g., mycotic aneurysm); *minor* criteria are localized AGI features or fever $\geq$38°C, where AGI is the most likely cause. (ii) Radiological *major* criteria comprise increasing perigraft gas volume on serial computed tomography (CT) imaging or perigraft gas or fluid ($\geq$7 weeks and $\geq$3 months, respectively) postimplantation; *minor* criteria include other CT features or evidence from alternative imaging techniques. (iii) Laboratory *major* criteria comprise isolation of microorganisms from percutaneous aspirates of perigraft fluid, explanted grafts, and other intraoperative specimens; *minor* criteria are positive blood cultures or elevated inflammatory indices with no alternative source.

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Conclusion: This AGI definition potentially offers a practical and consistent diagnostic standard, essential for comparing clinical management strategies, trial design, and developing evidence-based guidelines. It requires validation that is planned in a multicenter, clinical service database supported by the Vascular Society of Great Britain & Ireland.

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INTRODUCTION

Vascular prostheses (grafts placed at open surgery, and endovascular stent-grafts inserted via "keyhole" techniques) are increasingly used to treat life-threatening aortic aneurysms, aortic dissection, and occlusive vascular disease. Device insertion is complicated by infection in 0.5—4% of cases, causing major morbidity, mortality, and economic cost.[1—4] Fundamental tenets of aortic graft infection (AGI) management are removal of the infected device, revascularization (either by an anatomic route, or an uninfected extra-anatomic route), and adjunctive antimicrobial therapy.[5] However, vascular prostheses are not designed for ease of removal and in the setting of infection, surgical explantation carries a mortality of 18—30%.[6—10] Conversely, and often despite prolonged antimicrobial treatment, mortality within 2 years can approach 100% if an infected endograft is left *in situ*.[6,11]

The diagnosis and management of AGI is highly complex, clinical manifestations are protean, and there is no "gold-standard" diagnostic test.[3,5] In the existing literature, radiological data are mostly descriptive, microbiology details are brief or incomplete, and there have been no well designed trials of the optimum antimicrobial agent(s), route of administration, and treatment duration.[5] The better surgical studies are mostly large case series and there are no randomized, controlled trials of surgical strategies. It is therefore unsurprising that, in contrast to the well-established evidence-based guidelines for managing infections of other surgical prostheses (e.g., joints, heart valves), these are lacking for AGI.[3]

Addressing this deficiency requires a standardized case definition. Although there is general consensus that AGI is diagnosed by a combination of clinical, radiological, and laboratory findings, where described in the methodology of a very small number of publications, diagnostic criteria lack precision and do not give sufficient "weight" to the most significant.[5,12,13] It is also important that any definition is useful in routine clinical practice, for example in situations where an infected device cannot be explanted and confirmatory microbiology is lacking. Here, criteria used to diagnose AGI are reviewed by an experienced, multidisciplinary group of clinicians and a formal case definition is derived by expert consensus.

METHODS

The Management of Aortic Graft Infection Collaboration (MAGIC) was established in 2013 and comprises vascular surgeons, infectious diseases physicians, microbiologists, and radiologists experienced in the management of AGI, from several English National Health Service (NHS) Trusts with substantial vascular services (Guy's & St Thomas' NHS Foundation Trust, Heart of England NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust, Royal Free London NHS Foundation Trust, and University Hospital South Manchester NHS Foundation Trust). The AGI case definition was primarily developed for the MAGIC clinical service evaluation database (supported by the Vascular Society of Great Britain & Ireland) by expert consensus and informed by a systematic literature review. A modified Delphi method was used in the planning and development process.[14] Individual members initially proposed diagnostic criteria for wider group discussion and review. Independent feedback and comments were then collated and potential criteria (and their precise definitions) were included, modified, or excluded by an iterative process. Retained criteria were also ranked as either "major" or "minor", depending upon the weight of opinion/evidence that they were considered to contribute towards making a definitive diagnosis of AGI. Consensus was reached following formally convened face-to-face group meetings, teleconferences, and e-mail communications (N.M.P. was chairperson).

Results of a systematic review of English-language publications between 1 January 2005 and 22 June 2016 informed the consensus process. (This was specifically undertaken for a separate but closely related project involving several of the authors: J.A.T.S., R.E.B. and N.M.P. comprise an ongoing management of vascular graft infection guidelines working party, representing the British Society of Antimicrobial Chemotherapy, the Vascular Society of Great Britain & Ireland, and MAGIC, respectively.) Database search terms and objectives included diagnostic factors required to define vascular graft infection. Details of the methodology and results are registered on the PROSPERO international prospective register of systematic reviews ["Diagnosis and management of vascular graft infection (VGI)", available at; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016038759].

O.T.L. and N.M.P. produced the first draft of the manuscript and made subsequent revisions. The finalized MAGIC consensus was also presented at a national conference on 1 April 2016 (Guy's & St Thomas' Aortic Graft Infection Symposium).

RESULTS

Diagnostic criteria were divided into three categories representing the key specialties that must work closely together in order to optimize clinical management of AGI cases and reflecting the composition of the expert group.

	CLINICAL / SURGICAL	RADIOLOGY	LABORATORY
MAJOR CRITERIA	• Pus (confirmed by microscopy) around graft or in aneurysm sac at surgery • Open wound with exposed graft or communicating sinus • Fistula development e.g. aorto-enteric or aorto-bronchial • Graft insertion in an infected site e.g. fistula, mycotic aneurysm or infected pseudoaneurysm	• Peri-graft fluid on CT scan ≥ 3 months after insertion • Peri-graft gas on CT scan ≥ 7 weeks after insertion • Increase in peri-graft gas volume demonstrated on serial imaging	• Organisms recovered from an explanted graft • Organisms recovered from an intra-operative specimen • Organisms recovered from a percutaneous, radiologically-guided aspirate of peri-graft fluid
MINOR CRITERIA	• Localized clinical features of AGI e.g. erythema, warmth, swelling, purulent discharge, pain • Fever ≥38°C with AGI as most likely cause	• Other e.g. suspicious peri-graft gas/fluid/soft tissue inflammation; aneurysm expansion; pseudoaneurysm formation; focal bowel wall thickening; discitis/osteomyelitis; suspicious metabolic activity on FDG PET/CT; radiolabelled leukocyte uptake	• Blood culture(s) positive and no apparent source except AGI • Abnormally elevated inflammatory markers with AGI as most likely cause e.g. ESR, CRP, white cell count

Figure 1. Aortic graft infection (AGI) is *suspected* in a patient with any isolated major criterion, or minor criteria from two of the three categories: clinical/surgical, radiological, or laboratory. AGI is *diagnosed* in the presence of a single major criterion, plus any other criterion (major or minor) from another category. *Note*. Where microbiological investigations identify potential "contaminant" organisms (e.g., coagulase-negative staphylococci, propionibacteria, corynebacteria, and other skin commensals) a minimum of (i) two intraoperative specimens, (ii) two blood cultures, or (iii) one intraoperative specimen plus one blood culture must be positive with an indistinguishable organism in each sample based on antibiograms or a recognized typing method, e.g. pulsed-field electrophoresis. CT = computed tomography; FDG = fluorodeoxyglucose; PET = positron emission tomography; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

Diagnostic criteria were also ranked as either "major" or "minor" within each category. Fig. 1 shows a summary of the results. AGI is *suspected* in a patient with any isolated major criterion, or minor criteria from two of the three categories: clinical/surgical, radiological or laboratory. AGI is *diagnosed* in the presence of a single major criterion, plus any other criterion (major or minor) from another category.

Clinical/surgical criteria

The problems posed by the nonspecific nature of the many clinical manifestations of AGI were discussed. Although often absent, localized clinical features of AGI may simply represent postoperative wound inflammation or superficial soft tissue infection rather than graft involvement per se. Lack of specificity was also considered problematic with fever $\geq$38°C and it was therefore included with the additional caveat of a requirement for no other clinically apparent focus of infection. Both were consequently designated minor diagnostic criteria, but others proposed were not retained following discussion. In particular, systemic clinical features of sepsis (e.g., "septic shock") may result from any bloodstream infection, irrespective of whether or not AGI is the primary focus. Furthermore, determination of "systemic inflammatory response syndrome" relies upon the presence of other minor/nonspecific criteria (e.g., elevated blood white cells and fever $\geq$38°C).[15] Although anorexia, weight loss, lethargy, and malaise are common manifestations of AGI, they were also considered insufficiently specific for inclusion

The finding of visible intraoperative "pus" directly around a graft was initially proposed as convincing evidence of infection, but, following discussion, it was acknowledged that fluid with a similar "cloudy" appearance might be present for noninfective reasons, particularly if subsequent cultures prove to be negative. This major criterion was therefore modified to include the demonstration of pus cells by direct microscopy. Although an additional burden on the laboratory, microscopy is simple to perform and provides objectivity. In addition, it was agreed that AGI can also be strongly inferred if there is direct communication between a nonsterile site and the vascular prosthesis itself, including the following situations: fistulae (e.g., aortoenteric or aortobronchial), exposed grafts in deep open wounds, and deployment of an endovascular stent-graft into an already infected field (e.g., mycotic aneurysm).

Radiological criteria

In general, computed tomography (CT) was considered the first-choice imaging modality and the standard that others are compared against. Gas-forming organisms resulting in perigraft gas formation and rapid expansion of the aneurysm sac on serial scans was considered major evidence of AGI, but the principal limitation in routine practice is differentiating typical postoperative appearances from

those representing infection. The key question is, therefore, when does normal become abnormal? Unfortunately, exactly at what point in time after surgery the presence of perigraft gas or fluid is suspicious of AGI has been imprecisely defined in the literature. Reports are also without reference to a diagnostic standard and do not include specificity/sensitivity data. Noting these limitations, perigraft gas is rare beyond 1 week after surgery but appears to indicate AGI after 4–7 weeks.[16,17] Similarly, persistent perigraft fluid up to 3 months after surgery is not atypical but highly suspicious thereafter.[16] It was concluded that CT-guided aspiration of perigraft fluid for microbiological analysis should be undertaken in this situation but therapeutic placement of drains generally avoided in order to avoid introducing infection.[18–20]

Radiological findings that were considered to be minor criteria, requiring other evidence of AGI because of their subjective nature, include descriptions of perigraft soft tissue abnormalities such as "phlegmon" (an ill-defined inflammatory mass without overt abscess formation) and "stranding" (abnormally increased fat attenuation).[21–23] Secondary involvement by contiguous spread of infection involving adjacent structures may also, for example, cause hydronephrosis, focal bowel wall thickening, psoas abscess, and vertebral osteomyelitis/discitis but require the presence of major features to conclude AGI definitively.[18,22] Although a well-recognized feature of AGI, pseudoaneurysms may also occur for noninfective reasons such as dehiscence of a suture line. Finally, AGI is unlikely to be confused with primary large vessel vasculitis, which is rare in comparison, not typically localized to the region around a stent-graft, and associated with uniform mural thickening that is not characteristic of infection.[24]

With regard to the utility of other imaging techniques, magnetic resonance imaging has not been evaluated as extensively as CT but may be more sensitive in detection of inflammatory changes (e.g., in the psoas muscle) and can distinguish hematoma from perigraft fluid.[18,25] The sensitivity of technetium-99m/indium-111-labeled leukocyte imaging has been suggested to approach 100%, but false positivity is an issue and CT (or single-photon emission CT/CT if available) is usually required to delineate the significance of abnormal uptake consistent with focal infection/inflammation.[18,25,26] ^{18}F-fluorodeoxyglucose positron emission tomography (PET)/CT shows promise, but careful interpretation is required as prosthetic grafts can also provoke chronic low-grade inflammation for several years after surgery with associated diffuse tracer uptake.[27] The pattern of tracer uptake (focal as opposed to diffuse) together with ancillary findings on the CT component of the PET can improve diagnostic accuracy.[28–30]

Laboratory criteria

Culture of microorganisms from surgically explanted grafts or other intraoperative specimens (e.g., pus, tissue) was considered to be robust evidence of infection and therefore a major diagnostic criterion. Similarly, as a percutaneous aspirate of perigraft fluid/pus using radiological guidance entails an aseptic technique that minimizes contamination, positive microbiology from such samples is highly suggestive of AGI. Where standard laboratory culture is negative, for example, owing to the fastidious nature of the organism or prior antibiotic use, highly sensitive molecular techniques (e.g., "broad range" polymerase chain reaction to identify microbial DNA) were considered to have significant diagnostic value. There was insufficient data and experience to comment on other nonculture advancements in microbiological diagnosis, for example matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF).

Compared with high-virulence pathogens that would rarely be regarded as clinically insignificant (e.g., *Staphylococcus aureus*), isolation of possible contaminant organisms (e.g., skin flora, including *Staphylococcus epidermidis*, *Propionibacterium* spp. etc.) was felt to require additional levels of stringency in order to interpret their true significance. For a robust diagnosis, it is proposed that at least two samples (blood cultures and/or intraoperative specimens) must be positive with an indistinguishable organism in each (e.g., based on the antibiogram or a recognized typing method such as pulse-field electrophoresis).

While blood cultures may be negative in more than half of AGI cases, repeated isolation of the same organism in multiple samples is a classic feature of an endovascular infection.[5,11] In contrast to other microbiological diagnostic criteria, positive blood cultures were considered minor criteria as they do not provide direct, site-specific evidence of AGI, and their significance depends upon how confidently alternative sources can be excluded. The use of blood inflammatory markers as corroborative evidence for AGI was proposed, but these were also classed as minor criteria because they are nonspecific and typically elevated in the immediate postoperative period and multiple other concurrent, noninfective conditions. In contrast, it was felt that the diagnosis of AGI is questionable if inflammatory indices are completely normal.

DISCUSSION

AGI is an extremely complex clinical challenge and likely to be encountered more frequently in the future. Mortality from AGI is high, and diagnostic and treatment approaches differ significantly from center to center, with variable outcomes at present. Unfortunately the production of clinical guidelines is hampered by the lack of an agreed case definition, which is essential for designing high-quality clinical trials and evaluating evidence from research studies. A paucity of eligible publications in a systematic literature review justifies an approach based upon expert consensus at the present time. This is the first report proposing a definition of AGI, involving a formal, multidisciplinary, consensus process.

It has been postulated that the diverse range of pathogens causing AGI divide into two groups, which are dependent upon the nature of the clinical presentation and time elapsed since graft insertion.[5,31] "Early"

infections (<4 months) involve virulent organisms introduced at the time of surgery (e.g., *S. aureus*) and tend to produce an abrupt-onset, more toxic clinical picture with high fever. In comparison, "late" infection (>4 months) typically runs a more mild, subtle, and chronic course, reflecting the more indolent nature of the pathogens involved (e.g., skin flora). In reality, the distinction is much less clear cut and other factors are also important, for example AGI with aortoenteric fistulae are frequently polymicrobial owing to involvement of gut commensals including anaerobes and fungi. Although no pathogen is identified in many cases, there are some parallels that might be helpfully extrapolated from prosthetic joint infection where multidisciplinary collaboration has produced universally accepted diagnostic standards and management algorithms over the last decade.[32] Standard practice is to obtain at least three, and optimally 5–6, intraoperative samples in order to improve the diagnostic yield and help determine the significance of possible "contaminant" organisms. In addition sonication has been used to improve isolation of pathogens from explanted joint prostheses by disruption of bacterial biofilm, but its benefit remains unknown in AGI.

Potential limitations are acknowledged with some minor criteria necessitating an unavoidable degree of subjective judgment. Specifically, these include the interpretation of certain imaging (e.g., perigraft "stranding", rapid aneurysm expansion, increased metabolic activity on FDG-PET/CT or radiolabelled white cell accumulation) and those requiring that causes other than AGI be excluded (i.e., raised inflammatory indices, fever, localized clinical features, and positive blood cultures). Further validation of these criteria is needed but in particular it is worth noting that the Centers for Disease Control central venous device infection definition also entails a similar process of eliminating alternative sources for positive blood cultures.[33] Moreover it has also been proposed that any bacteremia, irrespective of source and within 4 weeks of graft implantation, should automatically be regarded with suspicion owing to the likelihood of hematogenous "seeding" to the prosthetic luminal surface before endothelial coverage is presumed to have occurred.[5]

Notwithstanding significant deficiencies in the published evidence and in order to define a necessary time point "cut-off", the recommendation that AGI should be strongly suspected if CT demonstrates perigraft fluid at ≥3 months post-graft insertion was considered reasonable and consistent with clinical experience.[18] This criterion is not 100% specific as fluid has very exceptionally been reported at 1 year without AGI,[19] but such limitations highlight the importance of no single feature being diagnostic and the requirement for corroborative evidence from other categories to fulfill the definition. Although not universally available, research is currently underway to determine the utility of ^{18}F-FDG-PET/CT, which has significant potential in improving diagnosis of AGI and monitoring response to treatment.[27–29]

In addition to comparing the range of diagnostic and treatment approaches employed by several English NHS vascular services in the management of AGI, the proposed case definition will be examined in a forthcoming multicenter service evaluation database, supported by the Vascular Society of Great Britain & Ireland. The intention is to invite wider participation from other vascular services upon completion of the five-center pilot project, and further aims include development of audit standards, best practice guidelines, and identification of key questions for future research studies. Finally, the creation of a national AGI registry is an important next step forward in improving patient management but requires a robust AGI definition to determine eligible cases for entry.[34]

CONFLICT OF INTEREST

J.A.T.S., R.E.B., and N.M.P. comprise a management of vascular graft infection clinical guidelines working group sponsored by the British Society of Antimicrobial Chemotherapy and Vascular Society of Great Britain & Ireland.

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