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Arteriovenous Access Graft Infection: Standards of Reporting and Implications for Comparative Data Analysis

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Abstract

There is presently a lack of organization and standardized reporting schema for arteriovenous graft (AVG) infections. The purpose of this paper is to evaluate the various types of treatment modalities for access site infections through an analysis of current publications on AVG. Key proposals are made to support standardization in a data-driven manner to make infection reporting more uniform and thereby facilitate more meaningful comparisons between various dialysis modalities and AVG technologies.

Keywords: arteriovenous graft; infections; hemodialysis; classification; management

Introduction

Hemodialysis (HD) is a complex attritional disease state that leads to a 45% annual increase in excess mortality.(1) Perhaps uniquely, the outcome and morbidity of HD is inherently related and may be altered through the method of providing HD, whether it is through a central venous catheter (CVC), arteriovenous fistula (AVF), or arteriovenous graft (AVG).(2, 3) Renal transplantation is the ultimate form of renal replacement therapy (RRT) with dramatic benefits in morbidity, survival and cost of treatment.(4, 5) However only 20% of patients requiring RRT are suitable for transplantation, and eligible patients often face significant delays of 3-4 years.(6) In particular, patients over 65 years of age are much more likely to die than receive a transplant.(7, 8) Thus for the vast majority of patients requiring RRT, the method by which dialysis is provided is the most significant modifiable factor in morbidity, mortality, and cost of providing health care.

It is widely accepted that the optimal method of providing vascular access is through a native AVF due to the best long-term patency, low complication and re-intervention rates, and better long-term patient survival than alternative methods such as a CVC.(9) However, there is significant variability within and among countries in the numbers of patients who rely either partly or wholly on CVCs.(10) Thus, CVCs remain important in access provision, with over 60% incidence and 30% prevalence.(11) There are many reasons why CVCs remain in widespread use, but several units in registry analysis have shown that a CVC-free policy for prevalent patients is possible with nearly 95% of patients using an AV access.(12, 13) Whilst this remains a potential goal for incident patients, the problem of prevalent patients on a CVC remains complex due to hostile anatomy, central vein stenosis, a reluctance to change established access modality, and lower autologous access success rates in patients already dialyzing through a CVC.(14)

Arteriovenous grafts (AVG) provide an alternative to AVF or CVC, with long-term survival outcomes that approach those of an AVF, along with better primary patency.(15) Their use has been limited by two main concerns: graft patency and infection. Patency concerns have been addressed in several reviews with a clear short

and medium term survival advantage to AVG over AVF when analyzed on an intention to treat basis.(15, 16) Other than primary patency, the use of grafts has been limited by the perceived risk of graft infection.(17) Several new grafts with more refined properties, such as permitting immediate cannulation, heparin bonding, tapered designs, spiral flow etc. have been brought to the market. Given that these grafts will be judged by historical comparators, a more rigorous approach to recognition and reporting of graft infection is warranted.

In general, access-related infection in the RRT cohort remains a leading cause of hospital admission, morbidity and mortality.(18) Although infection in a unit may be reported in a general context e.g. staphylococcus aureus bacteremia rates, the method of reporting infection by modality of access is not standardized. This makes it difficult to compare infection rates in new modalities and types of grafts. This paper aims to consider the approach to infection in the HD population, and consider historical data and more modern outcomes from studies of AVG. The authors have considerable experience in considering the role of AVG in vascular access, with over 1,500 cases of AVG implantation procedures between them. A series of proposals are made based on the authors experience in trying to determine what the role of AVG is in contemporary practice.

The Limitations of Contemporary Literature

Early reports of graft outcomes mainly comprised of observational studies from single centers with the larger series coming from the USA (Table 1). With newer products being released, case-series and eventually randomized trials have added to the literature (Tables 2 and 3). It is difficult to make a quick comparison between these highly selected case-series with variable or unreported follow up and randomized trials with end-points that are based on patency rather than infection, often using several methods of reporting from crude incidences to a rate by time. The current state of the literature is reminiscent of the confusion around CVC infection a decade ago with several new modifications to line design and many studies of strategies to prevent line infection. Eventually a robust definition of line infection and a standardized method of reporting have been developed.(19) Similarly graft patency

has been more robustly defined into primary, primary assisted and secondary patency.(20) The literature currently has several weaknesses that can be categorized, and a solution to these weaknesses is proposed.

1. Defining the Patient Cohort

a. Change in Dialysis Population: Perhaps as dramatically as the expansion in numbers over time, is the change in demographics of the RRT population with an increase in the older age groups, with considerably more comorbidity.(21) Multiple large observational studies of CVC infection have shown that the risk of infectious complications is related to the case-mix, with a four-fold higher infection rate in the older and diabetic (DM) populations.(22, 23) Thus, it is important that the case-mix of a population is defined to ensure valid comparison in considering AVG infection rates between reports.

Proposal: A core dataset of comorbidities should be included for all studies that report infection in grafts (including age, gender, ethnicity, DM, other sources of infection, immunosuppression, and previous RRT).

b. Inclusion and Selection Bias: AVGs are rarely implanted as a first access procedure in patients in whom there is a good AVF option, with an inevitable selection bias when considering outcomes. In addition, there is also considerable heterogeneity within the group of patients in whom an AVG is placed: the graft may be straight or looped, may have upstream complicating factors such as central vein stenosis or pacemaker wires, may be in the upper or lower limb, and may be placed due to other complications of access such as line infection or AVF thrombosis. Further, there may be considerable morphological differences in the artery of origin and the target vein for outflow. It seems likely that each of these factors would have some impact on patency and infection, though few studies have had the power to reflect on these subtleties. Nearly all case series of new products in whom an optimal outcome is desired have been in more favorable conditions such as the upper limb. A few older single-center series have had sufficient numbers and follow-up to allow some insights into the impact of these technical considerations.(24, 25) For example,

loop grafts may have better primary patency than straight, and infection rates in the lower limb may be worse, although variability in these results has been reported.(26, 27)

Proposal: Factors that may influence outcome should be reported in a standard fashion and should include donor artery to recipient vein, configuration, extremity, history of prior surgery, and history of trauma to the region.

2. Defining the Outcomes

a. Definition: The definition of a graft infection is vague and may range from a subjective mild cutaneous erythema treated effectively by oral antibiotics to significant pus-producing graft body infection that requires explantation. It is imperative that a robust and objective definition is universally employed, similar to that with CVCs. The definition must utilize a culture-proven bacteremia (CPB) in a clinical context that impacts treatment.

Proposal: Graft infection should be classified into either a suspicion (clinical scenario that is then translated into a clinical treatment) or a proven infection (culture-proven bacteremia plus clinical scenario that mandates treatment), with both rates being quoted. Rates should be presented as number of cases per 1,000 patient days so that comparisons can be made with the infectious disease literature.

b. Management and Outcome of AVG Infection: There are four RCTs that compare AVG to native AVF.(28-31) It could be anticipated that native AVF will have lower implantation infection rates, similar infections related to needling hematoma, but a higher salvage rate from infection. Successful management by localized excision of infected needling sites has been successfully reported, however the salvage rate after episodes of AVG infection as a whole remains unknown.(17) As a consequence of non-standardized reporting in clinical trials, the clinical sequelae of AVG infections and their varying severity remains relatively unknown.

Proposal: In addition to rigid criteria for diagnosing infection, it is imperative that the treatment and outcome of infective episodes is reported to allow an understanding of the impact of graft infection (AVG preservation, revision or loss).

Infection categorization: Pulling points a. and b. together, a system to record and categorize AVG infection is proposed: the Graft Sepsis Management (GSM) framework. This allows determination of the extent of infection and the consequences to the graft itself.

Graft	**Sepsis**	**Management**
1 - Localized Cellulitis	0 - No culture proven bacteremia	0 - No treatment required
2 - Localized Purulent Infection	1 - Culture proven bacteremia or metastatic infection	1 - Antimicrobial treatment only
3 - Diffuse Cellulitis	2 - Culture proven fungaemia	2 - Operative intervention with graft salvage 2a. Simple drainage only 2b. Local excision + rerouting of AVG 2c. Complex preservation procedures e.g. flap coverage
4 - Diffuse Purulent Infection		3 - Removal of graft

i.e. a localized needle site purulent infection requiring excision of a segment of graft without systemic infection would be recorded as G2S0M2b. This system allows for recording of both the extent of infection as well as the outcome for the patient and graft in a hierarchical manner, comparable between multiple studies.

c. The Natural History of Graft Infection: The etiology of graft infection and thus a basis for categorization may be elucidated from large case series that report infection over time. Harish et al. reported a large case-series of infections (40 in the leg and 92 in the arm).(27) Although there was no clear difference in infection rate between the upper and lower limbs, the rate of infection showed a distinct pattern: an early (less than four weeks) exponential rise in infections, followed by a continued linear increase over time. It seems likely that this reflects initial perioperative infection either during the procedure or seeding a perioperative hematoma following the procedure: a primary graft infection.

The longer term continued linear infection rate reflects the majority of infections occurring from cannulation: secondary infection. This group may also have a few delayed presentations of primary graft infection. Lafrance et al. and Bachleda et al. both report data that supports this theory in that 60% of graft infections occurred following needling.(32, 33) Finally, there are reports of occluded grafts presenting late as a source of occult sepsis: tertiary infection. It is uncertain how common tertiary infection is due to wide variation between series.(17, 25, 34) Ryan et al. found that 47% of graft infections occurred within four weeks, 39% at 2-6 months, and 14% at >6 months.(17) Beathard et al. found that 36 out of 100 thrombectomy specimens from occluded grafts grew organisms on culture, one explanation being that the method of diagnosing graft occlusion was repeated needling rather than auscultation.(35) Indeed, not enough is known about the relevance of the specific organisms commonly identified (e.g. Staphylococcus aureus versus coagulase negative staphylococci) in graft infections, and whether different treatment modalities can be utilized to manage these (e.g. salvage versus excision). As each of these infection types will lead to differing strategy changes in order to minimize infection rates, it is imperative that data on etiology, organism and root cause be gathered.

Proposal: All graft infections should be classified according to etiology (primary secondary, tertiary), organism and root cause.

d. Metric of Reporting: There is currently no universally accepted metric of reporting AVG infection. Older case-series report crude incidences that do not make any allowance for the duration of exposure to risk. Data on follow-up is absent or variably reported making meaningful comparison difficult e.g. Ryan et al. reports an infection rate of 3.4% in 1,441 patients with a mean follow-up that is not explicitly reported, but estimated at five years.(17) Even more recent reports such as that of Bachleda et al. reported an infection rate of 28.3% in 53 AVG with no follow-up or days of exposure reported.(36)

This is more robustly reported in contemporary case-series of new products, for example in reported case-series of Flixene, the reported incidence of infection ranges from 0 to 20%.(37) Three recent case series of Acuseal reported an infection rate between 0 and 0.2/1,000 hemodialysis days (HDD).(13, 38, 39) It is difficult to directly compare these rates and that of other case-series of Omniflow for example, with reported infection rates of 0 to 1% per year.(24) Many RCT similarly report an incidence per year, but often these are as descriptive data rather than a defined and powered end-point of the studies. It may be possible to apply a conversion factor based on the numbers, median days follow up and numbers of infections, but this involves considerable assumptions and post hoc analysis with inherent weaknesses. The lack of a defined method of reporting AVG infection significantly limits the ability to determining absolute and relative risks of differing types of AVG and more importantly, the comparison with alternative methods of RRT.

Proposal: all infections in reports of AVG should report infection as a standardized rate per 1,000 days exposure risk (HDD), similar to that now applied to CVC. This is a quantifiable and comparative measure that allows more rigorous comparisons to be made. Perhaps most importantly this allows a method of analyzing infection in a whole dialysis population in an intention-to-treat basis, rather than an artificial allocation into AVF/AVG/CVC that fails to reflect the evolving personal journey of access that often migrates between modalities.

3. Defining the Context: Much attention is placed on very precise outcomes from grafts such as patency. However vascular access must be obtained and the basis of considering outcomes should not be isolated from the alternatives available at that time. Quality of care outcomes should therefore consider not only patency and infection, but also procedure number and intensity, cost, hospitalization and impact on quality of life. Isolated reporting of AVG outcomes means little without considering the outcomes of alternative strategies for that patient cohort. By considering the outcome of strategies rather than procedures, and supporting this with more accurate information on the impact these strategies on the health services and patients, a more rounded measure of quality may be determined.

Proposal: Outcomes of strategies in patient groups should be considered in addition to outcomes of procedures alone. AVG use in patients with exhausted native options may be a personal access solution.(39) Reporting patency alone under these circumstances does not provide an accurate measure of success, without a valid comparator such as a CVC, nor convey if any benefit is to be gained for the patient in terms of hospitalization, number of procedures or quality of life.

4. New Products: Technical advances in recent years have led to new products with unique selling points. These advances are often marketed on the basis of animal studies and rely on limited case-series to support their clinical use. The use of RCT to compare AVG is rare, with only five RCTs published.(40-44) Only one product tested in these trials was marketed on the basis of lower infection rates – BCA, and surprisingly the infection rates reported were similar in the two arms.(43)

Proposal: RCT of grafts that promote lower infection rates as a key feature should be powered to detect significant changes, with other biases minimized.

5. Novel Approaches: It has long been attempted to utilize a more ‘natural’ approach to graft design and there are two main methods in production. Decellularized grafts rely on biological materials and graft manufacture to reproduce a ‘naturalistic’ conduit either from other natural conduits (bovine carotid artery, bovine ureter) or

allowing biological manufacture in animals (Omniflow) or human aortic stem cells.(45) In addition, modern nanotechnology has the potential to add biological properties to prosthetic grafts such as heparin bonding, antimicrobial incorporation such as silver and triclosan, and more recently biologically active grafts that have miRNA delivery, NO production, or implanted endothelial cells. This holds great promise if a clear target for improvement can be identified.(46-48)

Proposal: Given the vast resources directed at improving the options available for patients requiring RRT and the difficulty in funding and performing adequately powered RCT, it is essential that observational studies provide accurate comparative data that applies standard methods of reporting. In addition, proposals for graft registries of graft outcomes must be non-selective, comprehensive, allow for case-mix and alternatives and not institutionally based. Without anonymity of patients and surgeons, participation will inevitably be selective with limited conclusions possible.

Conclusion:

AVG survival and morbidity is principally determined by a combination of patency and infection complications. Standardization of AVG infection reporting is essential to facilitate meaningful comparison between RRT modalities and various AVG technologies.

A core data template of methodology of recording and reporting in AVG trials could be designed that would include:

1. Detailed demographic recording. A core dataset including age, diabetes, current HD status, time on HD, the presence of CVC, and if an AVG is being placed due to exhaustion of native options.
2. Infection categorization: In collecting the data on infection episodes, each case should be categorized using the proposed GSM system, with additional documentation regarding aetiology Primary (procedure related), Secondary (cannulation related), Tertiary (occluded graft presenting late as source of sepsis)) and organism.

3. Overall infection rates reported as a standardized rate per 1,000 days exposure (pre-dialysis + hemodialysis days).
4. The outcome of infection on graft survival. Graft survival curves should be performed of both primary (infection-free) AVG survival i.e. AVG that never develop infective complications for the duration of the study, and secondary (infection-treated) AVG survival i.e. AVG with treated episode(s) of infection, either medically or surgically, with maintained survival of all AVG for the duration of the study.

The main determinants of AVG survival are patency and infection. AVG infection should be reported and scrutinized as rigorously as patency. Without detailed reporting on AVG infection, meaningful comparison between various new technologies and RRT modalities is not possible. Furthermore, the understanding of the natural history of AVG infection, the consequences, and optimal treatment strategies cannot be advanced without rigorous recording and reporting of infection-related parameters. It is only though improving data collection and reporting that improvements in RRT can be delivered.

339 Table 1: Infection rates in single center case series.

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Author, Year	Number	% Upper Limb (UL)	Follow-Up	Infection Rate
Ryan 2004(17)	1,441	100%	? 5 y	3.5%
Ram 2010(26)	219	47% UL 53% thigh	Up to 8 y	0.5/ py; 17% 0.1 / py; 19%
Harish 2011(27)	1,309	78% UL 22% thigh	N.R.	92/1023: 9% 40/286: 14%
Bachleda 2012(36)	53	N.R.	N.R.	28.3%
Antoniou 2009(49)	15 study review	0%	N.R.	18%
Schild 2008(50)	702	N.R.	N.R.	9.5%
Allemang 2014(51)	265	92% UL	? up to 4 y	9%
Harlander-Locke 2014(52)	17 Bovine carotid arteries	Infected / risk	18 m	1/17; 6%
Chemla 2011(53)	Flixene (10) Rapidax (5)	100%	2 y	N.R.
Lioupis 2011(54)	48 Flixene	100%	1 y	6%
Scarritt 2014(55)	78 Trilaminate PTFE	100%	1 y	6%
Wijeyaratne 2011(56)	17 Avflo	100%	1 y	18%
Karatepe 2013(57)	24 Avflo	100%	1 y	4%
Ferraresso 2013(58)	10 Avflo	100%	6 m	0%
Peng 2003(59)	163 Vectra	100%	12 m	26.1%
Maytham 2015(60)	52 Acuseal	100%	533 d	16%

341 Notes. N.R.= not reported, y= year, m= month, d= day, py= patient year.

342 Table 2: Infection rates in Randomized Control Trials.

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Author, Year	**Number**	**% Upper Limb**	**Follow-Up**	**Infection Rate**
Rooijens 2005(28) RCT vs RCF	84 PTFE (RCF)	100%	1 y	1/84, 0.13 / py
Keuter 2008(29) RCT vs BTN	51 PTFE (BTN)	100%	325 d	6 early, 15%
Morosetti 2011(30) RCT	27 OmniflowII (30 BTN)	100%	2 y	0
Davoudi 2013(31) RCT	30 PTFE (30 BTN)	100%	N.R.	5/30; 17%
Dammers 2003(40) RCT	52 PTFE 4-7mm vs 57 PTFE 6 mm	100%	1 y	0.12 / py 0.03 / py
Ko 2009(41) RCT	47 Cuff PTFE 42 PTFE	100%	2 y	2/47, 4% 2/42, 5%
Kennealey 2011(43) RCT	26 BCA vs 27 cuffed ePTFE	100%	1 y	0.1 py BCA vs 0.13 py PTFE
Shemesh 2015(44) RCT	80 PTFE 80 Propaten	100%	23.5 m	3/80; 3.8% 3/80; 3.8%
Glickman 2001(61) RCT	71 Vectra 71 PTFE	100%	1 y	4/71; 5.6% 4/71; 5.6%

344 Notes. N.R.= not reported, y= year, m= month, py= patient year.

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347 Table 3: Infection rates in new products.

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Author, Year	Number	% Upper Limb	Follow-Up	Infection Rate
Desai 2019(13)	266 Acuseal	96%	24 m	1.2%
Palumbo 2009(24)	38 Omniflow	100%	3 m	0
Schild 2011(25)	33 Flixene	100%	6 m	6%
Chiang 2014(37)	45 Flixene 19 PTFE	100%	18 m	20% 40%
Tozzi 2014(38)	30 Acuseal	90%	6.3 m	0
Chemla 2011(53)	10 Flixene	100%	533 d	N.R.
Scarritt 2014(55)	78 Flixene	100%	12 m	9%
Maytham 2015(60)	52 Acuseal	100%	533 d	16%, (9% < 30 d)
Aitken 2014(62)	37 Acuseal	66%	N.R.	0.2/1000 HDD
Glickman 2016(63)	138 Acuseal	100%	12 m	11%
Tozzi 2016(64)	60 Acuseal	95%	542 d	3%
Wang 1996(65)	61 Omniflow 48 PTFE	63%	N.R.	1%/y 2.3%/y
Kakkos 2008(66)	76 Vectra	100%	18 m	6.6%
Berard 2015(67)	46 Flixene	73%	223.5 d	2%
Mistry 2013(68)	12 Flixene	100%	6 m	8%
Lioupis 2011(69)	48 Flixene	100%	N.R.	6%

349 Notes. N.R.= not reported, y= year, m= month, d= day, py= patient year.

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