

Outcome after endovascular stent graft treatment for mycotic aortic aneurysm: A systematic review

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Background: Surgical treatment for mycotic aortic aneurysms is not optimal. Even with a large excision, extensive debridement, in situ or extra-anatomical reconstruction, and with or without lifelong antibiotic treatment, mycotic aneurysms still carry very high mortality and morbidity. The use of endovascular aneurysm repair (EVAR) for mycotic aortic aneurysms simplifies the procedure and provides a good alternative for this critical condition. However, the question remains: if EVAR is placed in an infected bed, what is the outcome of the infection? Does it heal, become aggravated, or even cause a disastrous aortic rupture? In this study, we tried to clarify the risk factors for such an adverse response.

Methods: A literature review was undertaken by using MEDLINE. All relevant reports on endoluminal management of mycotic aortic aneurysms were included. Logistic regressions were applied to identify predictors of persistent infection.

Results: A total of 48 cases from 22 reports were included. The life-table analysis showed that the 30-day survival rate was $89.6\% \pm 4.4\%$, and the 2-year survival rate was $82.2\% \pm 5.8\%$. By univariate analysis, age 65 years or older, rupture of the aneurysm (including those with aortoenteric fistula and aortobronchial fistula), and fever at the time of operation were identified as significant predictors of persistent infection, and preoperative use of antibiotics for longer than 1 week and an adjunct procedure combined with EVAR were identified as significant protective factors for persistent infection. However, by multivariate logistic regression analysis, the only significant independent predictors identified were rupture of aneurysm and fever.

Conclusions: EVAR seems a possible alternative method for treating mycotic aortic aneurysms. Identification of the risk factors for persistent infection may help to decrease surgical morbidity and mortality. EVAR could be used as a temporary measure; however, a definite surgical treatment should be considered for patients present with aneurysm rupture or fever. (J Vasc Surg 2007;46:906-12.)

Mycotic aortic aneurysms are a rare subset (1%-1.8%) of aortic aneurysms.^{1,2} Despite advances in antibiotic treatment, purely medical management for mycotic aneurysms is often inadequate because of the possibilities of persistent infection, subsequent aneurysm rupture, and death.³ The gold standard management strategy remains surgical resection and debridement of the infected aorta and the surrounding tissues, the use of muscle flaps or omentum to cover the infected field, and either an in situ interposition graft or extra-anatomic bypass followed by long-term antibiotic therapy.^{3,4} However, surgical management in these patients possesses high surgical risks and mortality (13.3%-40%).³⁻⁶ Moreover, most patients with mycotic aneurysms have significant comorbidities, resulting in a lethal risk for major surgery.

In the past decade, endovascular aortic repair (EVAR) for thoracic or abdominal aortic aneurysms has become popular and has shown satisfactory results.^{7,8} Semba et al⁹ were the first to report successful treatment with EVAR in

three patients with mycotic aneurysms, and this was followed by several other similar reports.^{10,11} Such a treatment modality for mycotic aortic aneurysms would be simpler than the conventional procedure and may be effective for saving lives. Thus, it seems to be a very good alternative for treating patients with this critical illness. However, two questions arise: can the residual infection due to the lack of excision and debridement of the infected nidi be overcome with antibiotic treatment alone, and would the placement of a foreign body (EVAR) in an infected bed aggravate the infection? It is clear that the EVAR treatment for mycotic aortic aneurysms is not likely to be widespread unless these questions are answered.

We therefore conducted a systematic analysis of the reported cases of mycotic aortic aneurysms treated with EVAR to determine the incidence of and risk factors for persistent infection after treatment.

METHODS

Search strategy, data collection, and measurements of outcomes. We performed an English language search of MEDLINE from January 1980 to January 2007 through PUBMED by using the key words *infected*, *mycotic*, *aorta*, *aneurysm*, and *stent graft*. We also reviewed the references from the selected case reports. Twenty-five reports were thoroughly reviewed; two studies that did not provide any individual patient data and some duplicated reported cases were excluded. We extracted data in total from 22 reports that included 48 cases^{1,9-29} (Table I). All patients included in the study were carefully reviewed for clinical details

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Competition of interest: none.

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including age, sex, clinical presentation, symptoms, culture results, details of treatment, and early and late morbidity and mortality. We accepted the original author's definition of an aneurysm as mycotic and included patients who were culture negative. The healed patients were defined as those who did not have fever, signs of sepsis, or hemorrhage during follow-up. Treatment failure was defined as the presence of persistent infections, including persistent septicemia, uncontrollable sepsis, recurrent fistula with bleeding, and death secondary to persistent infection or complications of the mycotic aneurysms.

Primary data analysis. We analyzed the data by using SPSS release 11.5.0 (SPSS Inc, Chicago, Ill). The exploratory data analyses checked the distribution of values and for nominal data presented the results as a proportion (percentage) of the total. Differences between patients with persistent infection and those who had healed were evaluated by using the χ^2 test or Fisher exact test for categorical variables. A *P* value < .1 was considered statistically significant, and all the statistical tests were two tailed. We calculated the odds ratios (ORs) to assess the relationship between potential predictors and outcomes. Multiple logistic regression analysis was applied to adjust for confounding variables, to obtain adjusted estimates of the ORs and 95% confidence intervals (CI) for independent effects of the potential predictors, and to identify significant independent predictors of outcomes. The cumulative survival curve was calculated by using the Kaplan-Meier method.

RESULTS

Characteristics of the patients. The study group included 29 men and 19 women with a mean age of 63.85 years (range, 30-90 years) who had thoracic or abdominal mycotic aortic aneurysms treated with methods involving EVAR. The mean follow-up period for these patients was 22 ± 19 months.

The pathologic lesions were located in the thoracic aorta (*n* = 32) and abdominal aorta (*n* = 16). The reported pathogens involved included salmonella (*n* = 10), staphylococci (*n* = 10), streptococci (*n* = 3), mycobacteria (*n* = 3), and other species (*n* = 9), whereas in 13 patients the infecting organism was not identified. Most patients received broad-spectrum or sensitivity-specific antibiotics immediately when an infected aneurysm was suspected. Among these, 22 patients (45.8%) had received antibiotic treatment for more than 1 week before they received EVAR. Eighteen patients (37.5%) received emergency EVAR treatments because of symptoms of rupture, and in most of these patients, the bleeding stopped immediately after the EVAR procedure. Twenty-one patients (43.7%) had fever (body temperature >37.5°C) at the time they received the stent. Thirteen patients (37.1%) received related procedures in addition to their EVAR, including soaking stents in antibiotics, receiving drainage cannulas, and debriding with or without irrigation. Persistent infections occurred in 11 patients (22.9%), whose presentations included prolonged fever with no other symptoms (*n* = 1), uncontrolled sepsis (*n* = 7), and rupture or bleeding events

(*n* = 6). The 30-day mortality rate of EVAR treatment for mycotic aortic aneurysms due to sepsis or massive bleeding was 10.4% (five patients). Of the five late mortalities (10.4%), two died of cardiac disease, and three died with graft-related bleeding problems (Table I). In addition, the 12-month actual survival rate of the healed group was $94.0\% \pm 4.0\%$, and that of the persistently infected group was $39.0\% \pm 17.0\%$, a significant difference (Fig; *P* < .05).

Parameters for predicting persistent infection. We divided the 48 patients into 2 groups: the healed (*n* = 37) and those with persistent infection (*n* = 11). The median follow-up periods for the entire group, the healed group, and the persistent infection group were 15, 17, and 5 months, respectively. Various parameters relevant to the clinical outcome were analyzed (Table II). Univariate analysis identified the following parameters as significant predictors for persistent infection: age 65 years or older (OR, 7.39; 95% CI, 1.39-39.27), ruptured aneurysms (including those with aortoenteric fistulas and aortobronchial fistulas; OR, 4.14; 95% CI, 1.00-17.05), fever at the time of operation (OR, 4.92; 95% CI, 1.11-21.82), use of preoperative antibiotics for longer than 1 week (OR, 0.19; 95% CI, 0.04-1.00), and an adjunct procedure combined with EVAR therapy (OR, 0.65; 95% CI, 0.51-0.82). The last two parameters seemed to be protective factors. We further evaluated predictive parameters for persistent infection by using multiple logistic regression analysis by including all the predictors with a *P* value < .1 in the univariate analyses in a full model (Table III). From this we constructed the final model, which included only the predictors shown as significant in the multivariate analysis. The significant independent predictors associated with persistent infection in EVAR treatment for mycotic aortic aneurysms included rupture and fever at the time of operation.

DISCUSSION

Management of mycotic aortic aneurysms remains a challenging clinical problem for cardiovascular surgeons. Hsu et al³⁰ suggest that advanced age, infection with non-*Salmonella* species, and no surgical intervention are the major determinants for mortality in mycotic aortic aneurysms. Fillmore and Valentine³¹ determined that sepsis is the leading cause of death for surgical infected aneurysm patients and that a combination of host- and infection-specific variables may be more predictive of outcomes than any single risk factor. Discouraged by the high morbidity and mortality of standard surgical procedures in this disease, Semba et al⁹ first proposed EVAR as an alternate approach. Several subsequent reports suggest that EVAR in the management of mycotic aortic aneurysms provides a viable, less invasive alternative with favorable results.^{10,11,15} The procedure has significant advantages over open surgery as it avoids a large incision, full heparinization, extracorporeal circulation, aortic cross-clamping, interference with respiratory function, and the need for massive blood transfusion.³² However, putting an endovascular graft in an infected environment is controversial and against general surgical principles. If the infection

Table I. All cases summary

| Study | Patient age (y)/sex | Organism | Rupture | Site | Fever |
|--------------------------------|---------------------|-----------------------------|---------|------|-------|
| Ting ¹¹ | 87/M | SA | AEF | TAo | + |
| | 37/M | SA | No | TAo | + |
| | 59/M | <i>Salmonella</i> sp | No | TAo | + |
| | 68/M | <i>Candida albicans</i> | AEF | TAo | + |
| | 77/M | <i>Salmonella</i> | No | TAo | + |
| | 59/M | Not proven | AEF | TAo | + |
| | 90/M | Not proven | No | TAo | + |
| Alpagut ¹² | 38/M | SA | No | TAo | - |
| Forbes ¹³ | 73/M | <i>Salmonella</i> sp | No | AAA | - |
| | 83/F | <i>Salmonella</i> sp | No | AAA | - |
| Jorna ¹⁴ | 79/F | <i>Streptococcus</i> sp | CR | TAo | - |
| Lee ¹⁵ | 65/F | SA | No | AAA | - |
| | 58/M | GNB | No | AAA | - |
| | 56/M | TB | No | AAA | - |
| | 30/F | <i>Enterococcus</i> GNB | No | TAo | + |
| | 85/M | SA | AEF | AAA | + |
| Corso ¹ | 62/M | SA | CR | AAA | - |
| Gonzalez-Fajardo ¹⁶ | 75/M | Not proven | AEF | AAA | - |
| | 68/M | <i>Salmonella</i> sp | AEF | TAo | - |
| Sayed ¹⁷ | 46/F | Not proven | No | TAo | + |
| | 77/F | Not proven | ABF | TAo | - |
| | 50/F | Not proven | ABF | TAo | - |
| Jones ¹⁰ | 64/F | Not proven | No | TAo | - |
| | 62/M | Not proven | No | TAo | - |
| | 60/F | <i>Salmonella</i> sp | No | TAo | + |
| | 69/F | Not proven | ACF | TAo | + |
| | 72/F | Not proven | ABF | TAo | - |
| | 80/M | <i>Salmonella</i> sp | No | AAA | + |
| | 40/M | <i>Pneumococcus</i> sp | No | TAo | - |
| Koeppel ¹⁸ | 47/M | <i>Salmonella</i> sp | No | AAA | - |
| Kotzampassakis ¹⁹ | 84/F | <i>Salmonella</i> sp | ABF | TAo | + |
| Rayan ²⁰ | 51/M | SA | CR | TAo | - |
| Bell ²¹ | 76/M | SA | No | TAo | + |
| Stanely ²² | 64/M | <i>Streptococcus</i> sp | No | TAo | + |
| | 62/M | SA | No | TAo | + |
| | 77/M | <i>Enterococcus</i> sp | FR | TAo | - |
| | 79/F | <i>Streptococcus</i> sp | No | AAA | + |
| Van Doorn ²³ | 66/F | <i>Clostridium septicum</i> | AEF | TAo | + |
| Ischida ²⁴ | 81/F | SA | FR | TAo | + |
| Berchtold ²⁵ | 60/M | <i>Salmonella</i> sp | No | AAA | - |
| Bond ²⁶ | 58/F | Not proven | AEF | TAo | - |
| Liu ²⁷ | 42/F | TB | No | AAA | - |
| | 41/M | TB | FR | AAA | - |
| Madhavan ²⁸ | 50/M | SA | No | AAA | - |
| Kinney ²⁹ | 55/F | <i>Escherichia coli</i> | No | AAA | - |
| Semba ⁹ | 64/M | <i>Proteus mirabilis</i> | ABF | TAo | - |
| | 70/M | Not proven | No | TAo | - |
| | 69/F | <i>Clostridium septicum</i> | FR | TAo | + |

AEF, Aortoenteric fistula; ABF, aortobronchial fistula; ACF, aortocutaneous fistula; CR, contained rupture; FR, free rupture; fever, body temperature >37.5°C; MI, myocardial infarction; A/B, preoperative intravenous antibiotics taken for longer than 1 week; SA, *Staphylococcus aureus*; TAo, thoracic aorta; AAA, abdominal aorta; GNB, gram-negative bacilli; TB, *Mycobacterium tuberculosis*.

persists after EVAR, it is likely to produce subsequent irremediable disaster. For these reasons, the basis for successful application of EVAR for mycotic aneurysms interested us.

Several explanations have been proposed for the successful use of EVAR in mycotic aortic aneurysms. First, broad-spectrum antibiotics are administered as soon as a mycotic aortic aneurysm is suspected. This is usually followed by the appropriate antibiotics determined by culture and sensitivity testing, which might eradicate many bacte-

ria. Thus, many authors suggest that EVAR is feasible when antibiotic suppression has achieved negative blood cultures before surgery.^{10,33} Second, as reported by Jones et al¹⁰ and as indicated in our summarized data, no microbes could be isolated from blood and tissue cultures in 25% to 40% of mycotic aortic aneurysms. Third, the use of antibiotic-coated grafts to reduce the source of infection or of a coated endoprosthesis to release antibiotics into the blood stream has also been proposed to account for the success.^{14,22,32} Fourth, adjunct procedures such as surgical debridement or

Table I. Continued

| A/B | Adjunctive procedure | FU (mo) | Persistent infection | Mortality |
|-----|--------------------------|---------|-----------------------|------------------------|
| — | — | 3 | Sepsis | — |
| + | — | 38 | — | — |
| + | — | 35 | — | — |
| — | Thoracotomy, debridement | 34 | — | — |
| + | — | 7 | — | — |
| — | — | 3 | Stent-graft infection | — |
| + | — | 4 | — | — |
| + | — | 7 | — | — |
| — | — | 48 | — | — |
| — | — | 5 | Sepsis/bacteremia | — |
| + | Soaked in rifampicin | 6 | — | — |
| + | Drainage catheter | 36 | — | — |
| + | — | 48 | — | — |
| + | Drainage catheter | 96 | — | — |
| + | — | 0 | AEF/sepsis | <30 d |
| — | — | 0 | Rebleeding/sepsis | <30 d |
| + | — | 12 | — | — |
| — | — | 2 | Sepsis | 2 mp |
| — | — | 0 | Sepsis/bleeding | <30 d |
| — | — | 12 | — | — |
| + | Open aortotomy | 26 | — | — |
| — | — | 12 | — | — |
| — | — | 56 | — | — |
| — | — | 0 | — | <30 d (rupture) |
| — | — | 36 | — | — |
| — | — | 5 | Rebleeding | 5 mo |
| — | — | 28 | — | — |
| — | — | 27 | Rebleeding | — |
| — | — | 16 | — | — |
| — | Drainage | 12 | — | — |
| — | — | 6 | — | — |
| + | — | 7 | — | — |
| — | — | 42 | Persistent fever | — |
| + | Soaked in vancomycin | 12 | — | — |
| — | — | 15 | — | — |
| — | — | 10 | — | — |
| + | — | 2 | — | — |
| + | Debridement irrigations | 24 | — | — |
| + | — | 0 | Rupture, sepsis | <30 d |
| + | — | 48 | — | — |
| — | — | 62 | — | 62 mo (hematemesis) |
| + | — | 24 | — | — |
| — | Surgical drainage | 18 | — | — |
| + | Combine op excision | 12 | — | — |
| — | Drainage | 10 | — | 10 mo (MI) |
| + | Combine op excision | 25 | — | 25 mo (cardiac arrest) |
| — | Combined surgery AAA | 24 | — | — |
| + | Debridement | 4 | — | — |

Combine op excision, this surgery is combined with EVAR and open surgery excision for low abdominal aneurysm.

percutaneous drainage have been suggested to be protective and an important step in eliminating the source of infection.¹⁵ Finally, prolonged postoperative antibiotic therapy is also advocated as a key component for success,^{11,15} but there is no consensus on the optimal duration of antibiotic therapy. Most commonly, parenteral antibiotics are given for 2 to 8 weeks after surgery, but whether lifelong oral antibiotics are necessary is debated.^{4,15,17}

The clinical results after EVAR for mycotic aortic aneurysms—deduced from the accumulated data in this

report—show only 5 postoperative deaths (5/48; 10.4%) and 5 late deaths (5/48; 10.4%). Additionally, compared with the 70% 12-month survival rate in traditional surgical results of infected aortic aneurysm reported by Hsu et al,³⁰ an important observation is that the 12-month survival rate for the healed group after EVAR is 94%, thus suggesting that when successful EVAR treatment is achieved for mycotic aortic aneurysms, it might yield a better clinical outcome than conventional surgery.³⁻⁶ Furthermore, because up to 60% of mycotic aneurysms may present as ruptured,³⁴ EVAR can be used as a temporary measure to quickly

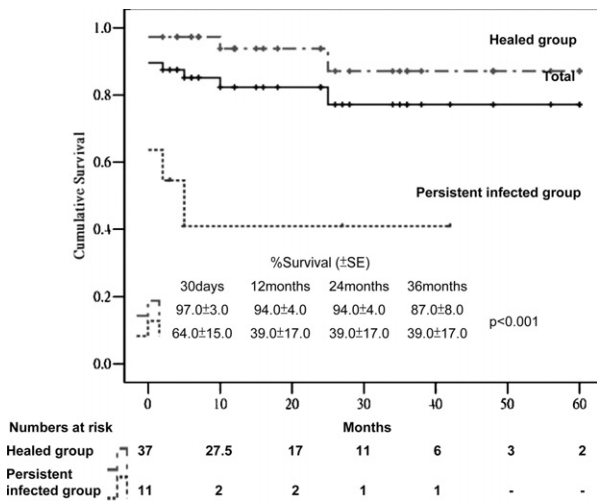


Fig. Actuarial survival of study subjects, calculated by the Kaplan-Meier method.

achieve hemodynamic stability and as a bridging measure to possibly allow further definitive surgical treatment.^{15,17,23}

Unfortunately, patients who showed persistent infection after EVAR treatment had a 12-month survival rate of only 39.0%. Thus, information that might allow identification of such patients predisposed to persistent infection after EVAR would be highly appreciated. Our univariate analysis revealed that age 65 years or older, ruptured aneurysms (including those with aortoenteric fistulas and aorto-bronchial fistulas), and fever at the time of operation are significant parameters related to the incidence of persistent infection in EVAR treatment for mycotic aortic aneurysms. Aging strongly correlates with a cluster of risk factors and with multiple organ dysfunction^{35,36}: just as age is an independent determinant of mortality in cardiac surgery, it also plays an important role in EVAR procedures. Lee et al¹⁵ pointed out that major factors contributing to unfavorable results of EVAR are the presence of aortoenteric fistula and active infection. A well-known axiom states that surgical treatment for ruptured aortic aneurysms car-

Table II. Demographics of infected aortic aneurysms treated by endovascular stent graft

| Variable | Persistent infection (n = 11) | | Healed (n = 37) | | P value | OR (95% CI) |
|----------------------------|----------------------------------|--------|--------------------|--------|---------|---------------------|
| | n | % | n | % | | |
| Male sex | 7 | 63.64% | 22 | 59.46% | 1.000 | 1.19 (0.30-4.80) |
| Age ≥65 y | 9 | 81.82% | 14 | 37.84% | .010 | 7.39 (1.39-39.27) |
| DM | 2 | 18.18% | 8 | 21.62% | 1.000 | 0.81 (0.14-4.50) |
| Heart disease | 2 | 18.18% | 11 | 29.73% | .702 | 0.53 (0.10-2.84) |
| Cancer | 2 | 18.18% | 5 | 13.51% | .653 | 1.42 (0.24-8.59) |
| Osteomyelitis | 1 | 9.09% | 5 | 13.51% | 1.000 | 0.64 (0.07-6.14) |
| Pain | 4 | 36.36% | 18 | 48.65% | .514 | 0.60 (0.15-2.42) |
| Positive culture | 8 | 72.73% | 27 | 72.97% | 1.000 | 0.99 (0.22-4.48) |
| Salmonella spp | 3 | 27.27% | 7 | 18.92% | .675 | 1.607 (0.337-7.658) |
| Ruptured aneurysm | 7 | 63.64% | 11 | 29.73% | .041 | 4.14 (1.00-17.05) |
| Diseased site (thoracic) | 4 | 36.36% | 12 | 32.43% | 1.000 | 1.19 (0.29-4.87) |
| Fever at operation | 8 | 72.73% | 13 | 35.14% | .027 | 4.92 (1.11-21.82) |
| Pre IV A/B | 5 | 45.45% | 26 | 70.27% | .163 | 0.35 (0.09-1.40) |
| Pre IV A/B >1 wk | 2 | 18.18% | 20 | 54.05% | .036 | 0.19 (0.04-1.00) |
| Post IV A/B >4 wk | 4 | 36.36% | 18 | 48.65% | .514 | 0.60 (0.15-2.42) |
| Adjunctive procedure | 0 | 0.00% | 13 | 35.14% | .023 | 0.65 (0.51-0.82) |
| Early complication | 7 | 63.64% | 8 | 21.62% | .022 | 6.34 (1.48-27.22) |
| 30-d mortality | 4 | 36.36% | 1 | 2.70% | .007 | 20.57 (1.99-212.72) |
| Late complication (n = 40) | 3 | 42.86% | 5 | 13.89% | .046 | 9.00 (1.19-68.13) |
| Late mortality (n = 40) | 2 | 28.57% | 3 | 8.33% | .180 | 4.40 (0.58-33.21) |

OR, Odds ratio; CI, confidence interval; DM, diabetes mellitus; Pre/Post IV A/B, preoperative/postoperative intravenous antibiotic use.

Table III. Predictive factors associated with persistent infection problems

| Risk factors | Full model, OR (95% CI) | Final model, OR (95% CI) | P value |
|----------------------|-------------------------|--------------------------|---------|
| Age ≥65 y | 7.39 (1.39-39.27) | — | |
| Ruptured aneurysm | 4.14 (1.00-17.05) | 7.93 (1.29-48.87) | .026 |
| Fever at operation | 4.92 (1.11-21.82) | 6.88 (1.07-44.14) | .042 |
| Protective factors | | | |
| Pre IV A/B >1 wk | 0.19 (0.04-1.00) | — | |
| Adjunctive procedure | 0.65 (0.51-0.82) | — | |

OR, Odds ratio; CI, confidence interval; Pre IV A/B, preoperative intravenous antibiotic use.

ries five times the rate of surgical mortality as elective procedures.³⁷ Aneurysm rupture indicates that the patient is in a critical condition and that the surrounding tissues may have been extensively damaged. These patients often need emergency treatment without the chance of any additional therapy. Fever at the time of operation indicates that patients have an active infection or that infection is not well controlled by antibiotics. By contrast, preoperative antibiotic use for longer than 1 week combined with adjunct procedures might have significant protective effects. The treatment protocol for infective endocarditis^{38,39} has shown us that if we can administer sufficient preoperative antibiotics to control the infection, surgical results will be improved.

Routine preoperative antibiotics might not completely suppress bacterial activity, whereas a longer period of preoperative antibiotics may have a better chance of eradicating the infection. Although postoperative antibiotics also do not guarantee that the foci of infection are eradicated, the results of EVAR in such situations are impressive.¹² Adjunct procedures assist in eliminating the infective foci to decrease the rate of persistent infection,^{15,22} but they might also indicate that patients are in a worse condition and need additional therapy to achieve the therapeutic goals. However, further multivariate analysis revealed that many of these factors interact and that ruptured aneurysms and fever at operation are the only significant independent predictors associated with persistent infection in EVAR treatment for mycotic aortic aneurysms.

CONCLUSION

This study summarized all cases of EVAR treatment for mycotic aortic aneurysms reported in the literature, analyzed the risk factors for occurrence of persistent infection, and followed up the clinical results of this technique. The most important finding of this meta-analysis is that persistent infection after EVAR treatment of mycotic aortic aneurysms is closely associated with a poor prognosis. From the results of the analysis, we identified aneurysm rupture and fever at operation as the most significant variables associated with the occurrence of persistent infection in these patients. When patients present with rupture or have fever, the EVAR method should be considered as a temporary measure to achieve hemodynamic stability. Additionally, if the fever persists after the EVAR, a definite surgical treatment should be considered. However, further multi-institutional and registry data are required to clarify the long-term outcomes of EVAR and to determine whether EVAR use in mycotic aortic aneurysms is as effective as or better than standard surgical care.

AUTHOR CONTRIBUTIONS

Conception and design: C-DK

Analysis and interpretation: C-DK, H-LL

Data collection: C-DK

Writing the article: C-DK, Y-JY

Critical revision of the article: C-DK, H-LL, Y-JY

Final approval of the article: C-DK, Y-JY

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Obtained funding: C-DK

Overall responsibility: C-DK, Y-JY

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