Incidence and associated risk factors of cancer in patients after infective endocarditis hospitalization: A propensity score matched analysis

Hung Yi Chen, M.D.1,2

BACKGROUND: The relationship between infective endocarditis (IE) and malignancies has been reported. However, cancer development is multifactorial and mortality is high in IE survivors. We aimed to estimate the absolute cancer risk in IE survivors and tried to find the potential risk factors.

METHODS: This nationwide, population-based cohort study evaluated 8649 newly diagnosed IE survivors who received aspirin after discharge from first hospitalization using the Taiwan National Health Insurance Research Data-base (NHIRD). Propensity score method was used in a 1:1 ratio based on age, gender, income, urbanization level, Charlson comorbidity index (CCI), concomitant medication, and medical history. The primary outcomes were all specific cancer types. All the variables matched for propensity score were analyzed to find their association with cancer occurrence.

RESULTS: Compared with the matched cohort, IE survivors increase the risk of cancer (adjusted hazard ratio [aHR], 1.64; 95% confidence interval [CI], 1.39-1.94), as well as significantly elevated risks of digestive (aHR, 2.27; 95% CI, 1.76-2.92) and hematologic (aHR, 2.73; 95% CI, 2.31-5.71) malignancies. Age (aHR, 1.47; 95% CI, 1.36-1.57), male (aHR, 1.49; 95% CI, 1.18-1.90), CCI score (aHR, 1.05; 95% CI, 1.01-1.10) are risk factors for cancer occurrence among IE survivors, while aspirin use reduced the cancer risk (aHR, 0.73; 95% CI, 0.54-0.98).

CONCLUSION: Our study provides further investigation between IE and cancer risk. In conclusion, cancer risk, particularly digestive and hematologic malignancies, is substantially increased in IE survivors. Our results also provide additional evidence that aspirin use is effective in reducing cancer risk in IE survivors.

Key Words: Infective endocarditis; Cancer; Propensity score match; Aspirin

Incidence and associated risk factors of cancer in patients after infective endocarditis hospitalization: A propensity score matched analysis

Chen HY. Incidence and associated risk factors of cancer in patients after infective endocarditis hospitalization: A propensity score matched analysis. Curr Res Cardiol 2017;4 (3):29-34.

BACKGROUND: The relationship between infective endocarditis (IE) and malignancies had been reported. However, cancer development is multifactorial and mortality is high in IE survivors. We aimed to estimate the absolute cancer risk in IE survivors and tried to find the potential risk factors.

METHODS: This nationwide, population-based cohort study evaluated 8649 newly diagnosed IE survivors who received aspirin after discharge from first hospitalization using the Taiwan National Health Insurance Research Data-base (NHIRD). Propensity score method was used at a 1:1 ratio based on age, gender, income, urbanization level, Charlson comorbidity index (CCI), concomitant medication, and medical history. The primary outcomes were all specific cancer types. All the variables matched for propensity score were analyzed to find their association with cancer occurrence.
NHRI, Taiwan. The NHRI secured the privacy of all beneficiaries and provided health insurance data to researchers who obtained ethical approval.

Study design

This nationwide population-based, observational, retrospective cohort study aimed to determine the association between IE and subsequent cancers. We enrolled two cohorts in the study: the IE cohort and a matched control. The IE cohort was conducted from January 2000 to December 2009. To confirm the diagnosis of IE, we extracted the cohort from the entire original NHIRD, consisted of first time discharged patients with an IE diagnosis (ICD-9-CM code: 421.0, 421.1, and 421.9) who received antibiotic treatment during hospitalization. The included reliable IE diagnosis was based on the revised Duke criteria (15). The agreement of code IE diagnosis in Taiwan NHIRD with other clinical definite or possible IE in a tertiary center in Taiwan had been validated (16). We excluded patient with the following characteristics: age >20 years, prior history of IE, and mortality during hospitalization for IE. Patients with malignancy diagnosis upon initial diagnosis of IE were also excluded. We defined the index date as the first day of discharge from IE. We extracted the control cohort from the Longitudinal Health Insurance Database, a subset of the original NHIRD, which contains data from a random sample of 1 million NHI beneficiaries. The exclusion criteria for the control cohort were the same as IE cohort. Index date for subjects in the control cohort were randomly assigned and corresponded to those patients in the IE cohort.

To avoid the influences of baseline differences as household income, urbanization level, concomitant medications, comorbidities, and coexisting condition, propensity score method was used with 1:1 matching and we calculated for the likelihood of hospitalization for IE using the baseline covariates and multivariate logistic regression analysis. One control patient was matched with each IE cohort patient with similar propensity score based on nearest neighbor matching without replacement using calipers of width equal to 0.1 standard deviation of the logit of the propensity score.

Outcomes

The main dependent outcome in this study was the primary cancer incidence in patients with IE. The diagnosis of cancer was identified using the records of the Catastrophic Illness Patient Database. The diagnostic codes of cancers were defined as those from 140 to 208.91 in the ICD-9-CM format. Malignant neoplasm of ill-defined sites (ICD-9-CM 195) and secondary cancers (ICD-9-CM 196-199) were excluded. We defined the index date as the first day of discharge from IE. Patients with malignancy diagnosis upon initial diagnosis of IE were also excluded. We defined the index date as the first day of discharge from IE. Patients with malignancy diagnosis upon initial diagnosis of IE were also excluded. We defined the index date as the first day of discharge from IE.

We included baseline demographic characteristics as age, gender, monthly income (NT$<19,100, NT$ 19,100-41,999, and NT$>42,000), urbanization, and Charlson Comorbidity Index (CCI) score. According to the Taiwan NHRI, urbanization levels in Taiwan are divided into four strata. The most urbanized areas are designated as level 1, and the least urbanized areas as level 4. Systemic health is determined by CCI score, and each increase in score indicates a stepwise increase in cumulative mortality (17). Other systemic diseases related to general health not included in the CCI were also evaluated including coronary artery disease, dyslipidemia, end-stage renal disease, arterial fibrillation, pre-existing valvular heart disease, and drug abuse. We also extracted concomitant use of medications that could be associated with cancer risk when discharge following IE as aspirin, clopidogrel, ticlopidine, and statin (8,18).

Statistical analysis

The baseline characteristics of the study cohorts were analyzed using descriptive statistics. The Pearson X² test was used to compare the baseline characteristics of the two cohort groups for categorical variables and the independent t-test for parametric continuous variables. Propensity score of the likelihood of IE were determinate by multivariate logistic regression analysis, conditional on baseline covariates (19). We used Cox regression models with a conditional approach using stratification to calculate adjusted hazard ratios (aHRs) and 95% confidence intervals (CI) for the risk of cancer in each group. Due to the high mortality rate in patients with IE, competing-risk regression using Fine and Gray's model was also performed (20). The Kaplan-Meier method was used to estimate the cumulative incidence of cancers, and the logrank test was used to evaluate the differences between the two cohorts.

Data linkage, processing, and sampling were done by the SQL Server 2012 (Microsoft Corporation, Redmond, Washington, USA). We used SAS version 9.3 (SAS Institute, Cary, North Carolina, USA) for propensity scores calculation. The STATA statistical software (version 12.0; Stata Corp, Texas, USA) was used for conducting all other statistical analysis. Statistical significance was defined as P < 0.05.

RESULTS

Demographic and clinical characteristics

During the study periods, 8,690 patients hospitalized for the first episode of IE between January 2000 and December 2009 were enrolled, including 5,766 (66.4%) males and 2,924 (33.5%) female, with the male to female ratio of 1.99:1. The mean age ±SD was 52.9 ±18.9 years in IE patients and 53.0 ±18.9 years in control patients. The male to female ratio of the IE and control groups were 66.4% and 33.6%, respectively. The differences in the baseline demographic characteristics are presented in Table 1.

AIDS 116 (1.3) 97 (1.1) 97 (1.1) 1
Cancer risk and associated risk factors in IE patients

| Drug abuse                              | 1,032 (11.9) | 966 (11.2) | 993 (11.5) | 0.943 |
|-----------------------------------------|--------------|------------|------------|-------|
| Valve replacement with mechanical valve | 856 (9.9)    | 851 (9.8)  |            |       |
| Valve replacement with bioprosthetic valve | 470 (5.4)    | 469 (5.4)  |            |       |

SD Standard Deviation; NT$ New Taiwan Dollars; AIDS: Acquired Immunodeficiency Syndrome

**TABLE 2**
Associations between infective endocarditis and risks of cancer

| Propensity Score–Matched | IE cohort | Control cohort | Crude | Competing risk† |
|--------------------------|-----------|----------------|-------|-----------------|
|                          | No. of Event | Person-years | Incidence rate* | No. of Event | Person-years | Incidence rate* | Hazard Ratio (95% CI) | Hazard Ratio (95% CI) | p Value | p Value |
| All All cancer           | 334       | 36798         | 90.77     | 244           | 44185         | 55.22         | 1.64 (1.39-1.94)      | 1.36 (1.15-1.60)      | <0.001  | <0.001  |
| Death                    | 3118      | 37421         | 833.23    | 1502          | 44636         | 336.5         | 2.41 (2.27-2.56)      | <0.001  |         |
| Male All cancer          | 236       | 24575         | 96.03     | 160           | 29064         | 55.05         | 1.75 (1.43-2.14)      | 1.46 (1.19-1.78)      | <0.001  | <0.001  |
| Death                    | 2040      | 25010         | 815.66    | 1003          | 341.86        | 341.86        | 2.33 (2.16-2.51)      | <0.001  |         |
| Female All cancer        | 98        | 12223         | 80.18     | 84            | 15121         | 55.55         | 1.43 (1.07-1.91)      | 1.16 (0.87-1.55)      | 0.017   | 0.316   |
| Death                    | 1078      | 12410         | 868.65    | 499           | 15296         | 326.22        | 2.57 (2.31-2.86)      | <0.001  |         |

*per 104 person-years.
†Adjusted for propensity score.
‡Death was calculated as a competing risk in this model.
Interaction p-value for sex was 0.298.
IE: Infective endocarditis, CI: Confidence Interval

Figure 1) Cumulative incidence of cancer among patients with infective endocarditis and control cohort

Gender ratio about 2.0. The mean age of the IE cohort was 52.9 (SD, 18.9) years. After propensity score matching, we enrolled 8,649 patients with IE and 8,649 matched cohorts in the study (Table 1).

Cancer risk in IE patients without previous history of malignancy

There were 334 patients diagnosed with cancer during the follow-up periods after discharge from hospitalization due to IE. The aHR for risk of cancer was 1.64 (95% CI, 1.39 to 1.94). The cumulative incidence of all cancer risk in patients with IE and the matched cohort was illustrated in Figure 1.

When stratified by gender, increased risks for all cancers remained in both males (aHR, 1.75; 95% CI, 1.43-2.14) and females (aHR, 1.43; 95% CI, 1.07-
TABLE 3
Associations between infective endocarditis and risks of cancer

| Type of cancer | No. of Event | Incidence rate | No. of Event | Incidence rate | Hazard Ratio (95% CI) | p Value |
|----------------|--------------|----------------|--------------|----------------|-----------------------|---------|
| All cancer     | 334          | 90.77          | 244          | 55.22          | 1.64 (1.39-1.94)       | <0.001  |
| Head and neck  | 30           | 8.15           | 19           | 4.3            | 1.93 (1.08-3.43)       | 0.025   |
| Digestive      | 172          | 46.74          | 92           | 20.82          | 2.27 (1.76-2.92)       | <0.001  |
| Eosophagus     | 17           | 4.62           | 2            | 0.45           | 1.63 (0.65-4.04)       | 0.296   |
| Stomach        | 11           | 29.89          | 8            | 18.11          | 2.56 (1.70-3.86)       | <0.001  |
| Colon and rectum| 71          | 19.3           | 34           | 7.7            | 2.04 (1.36-3.06)       | 0.001   |
| Liver and biliary tract | 64 | 17.39 | 38 | 8.6 | 1.18 (0.44-3.13) | 0.746 |
| Pancreas       | 8            | 2.17           | 8            | 1.81           | 0.93 (0.41-2.11)       | 0.856   |
| Lung and mediastinum | 27 | 7.34 | 27 | 6.11 | 1.20 (0.70-2.05) | 0.499 |
| Bone and soft tissue | 4 | 1.09 | 3 | 0.68 | 1.53 (0.34-6.86) | 0.574 |
| Bone and soft tissue | 7 | 1.9 | 2 | 0.45 | 4.06 (0.84-19.54) | 0.081 |
| Breast         | 10           | 2.72           | 13           | 2.94           | 0.93 (0.41-2.11)       | 0.856   |
| Genitourinary  | 44           | 11.96          | 62           | 14.03          | 0.84 (0.57-1.24)       | 0.389   |
| Cervix†        | 8            | 6.55           | 3            | 1.98           | 3.21 (0.85-12.10)      | 0.085   |
| Uterus†        | 0            | 0              | 3            | 1.98           | 1.81 (0.30-10.86)      | 0.515   |
| Ovary†         | 3            | 2.45           | 2            | 1.32           | 1.10 (0.56-2.18)       | 0.778   |
| Prostate†      | 16           | 6.51           | 17           | 5.85           | 0.59 (0.25-1.38)       | 0.224   |
| Bladder        | 8            | 2.17           | 16           | 3.62           | 0.36 (0.15-0.90)       | 0.029   |
| Kidney         | 6            | 1.63           | 20           | 4.53           | 0.43 (0.04-4.12)       | 0.462   |
| CNS            | 1            | 0.27           | 3            | 0.68           |                      |        |

*Adjusted all covariate lists in Table 1.
†Only female included in this analysis.
‡Only male included in this analysis.
IE: Infective endocarditis; CI: Confidence interval

When death was calculated as a competing risk in this model, the aHR was 1.36 (95% CI, 1.15 to 1.60). The associations between IE and subsequent cancer is shown in Table 2.

With regards to specific cancer types, the risk of head and neck (HR, 1.93; 95% CI, 1.08-3.43), esophagus (HR, 10.29; 95% CI, 2.37-44.56), colon and rectum (HR, 2.56; 95% CI, 1.70-3.86), liver and biliary tract (HR, 2.04; 95% CI, 1.36-3.05), and hematologic malignancies (HR, 2.73; 95% CI, 1.31-5.71) were significantly higher in patients with IE. The associations between IE and risks of different site of cancer are listed in Table 4.

Risk factors for cancer after the diagnosis of IE
In Cox multivariate proportional hazard analysis, age, per 10-year (HR, 1.47; 95% CI, 1.36-1.57), males (HR, 1.49; 95% CI, 1.18-1.90), and Charlson comorbid index score (HR, 1.05; 95% CI, 1.01-1.10) were independent risk factors for cancer in patients with IE. Aspirin use (HR, 0.73; 95% CI, 0.54-0.98) was a protective factor in this study.

DISCUSSION
Cancer process is multistage, and cancerous growth forms as the result of a sequence of events over a period of time. To reduce the influence of possible confounders in cancer development, propensity score method has been used to decrease possible confounders in studies for cancer risk (21,22). Clinically, IE patients have a high mortality rate both in-hospital and follow-up, and cancer process is slow and may take many years. It is difficult to assay the categorical relationship between the two diseases. In studying cancer risk and prognosis, death could be a potential factor influences the results. And competing mortality has been widely used in evaluating cancer risks and outcomes to minimize the effect (23,24). Our study demonstrates a significantly increased cancer risk in newly diagnosed IE patients than propensity score-matched group. Results of the current study show the increased risk in cancer occurrence in head/neck, digestive, and hematologic system. Our data also demonstrates the cancer risk in different cancer types, and suggests the cancer risk is prominent in digestive cancer, particularly in colorectal neoplasm. This is consistent with prior data. Cancer patients without clinical manifestation with compromised immunity could be vulnerable to IE (6,11). Increased the incidence of peri-diagnosis of IE in elderly cancer patients has been demonstrated (25). Despite the causal relationship is not clear, our results provide further evidence in the association between IE and cancer risk, and the risk remains high in 10-year follow-up. This is the first main finding in our study.
Cancer risk and associated risk factors in IE patients

Considering all of the variables include in Table 1 to find their association with cancer risk, the results show age, gender, CCI score increase the cancer risk. While aspirin use decreases cancer risk in IE survivors. This is another main finding in our study. Similar effect is not found in clopidogrel, ticlodipine, and statin use. Although true mechanism is uncertain, there were experimental, epidemiologic, and clinical evidences about aspirin use in lowering cancer development, particular for colorectal cancer (26). Some studies demonstrated aspirin use offered protection in esophageal and stomach cancer, despite the effect was not prominent as colorectal cancer (27). The effect of aspirin in reducing cancer risk of non-gastrointestinal tract also had been documented (28,29). As for IE, the benificent and risk of aspirin use has been researched, however, whether aspirin therapy is associated with better outcomes in IE patients remains controversial. In addition to the effect of embolic events prevention, some studies demonstrated aspirin use reduced vegetation enlargement and decreased occurrence of acute valve replacement surgery in IE patients, but without lowering cancer incidence (30,31). Investigations of IE are limited because IE is the disease with low incidence, hard for diagnosis, and the latency period between initial symptom and definite diagnosis. Although we do not perform specific cancer analysis, our data suggests aspirin therapy could lower overall cancer risk in IE survivors. As for the benefits and risks from aspirin in IE survivors, further assessment of the advantage and disadvantage is required. Our data also demonstrates decreasing cancer risks in drug abuse. We do not have any explanation for the result. We assume a condition that drug abuser may have less regular medical follow-up and record than general population, and has a less cancer detection rate. However, the true reason needs further evaluation.

Our study demonstrates cancer risk is high in IE patients with 10-year follow up, whether IE increases cancer risk or is a substantial marker for presence of occult cancer remains unclear. The major strengths of the current study are the case definition, its population-based design, 10-year study periods, and its complete coverage of IE and cancer patients in the population, wherein the possibility of loss to follow-up is essentially precluded. In addition, to reduce the effects of possible confounding, we use propensity score-matched control subjects in comparison with a general population. Some limitations of our study should be considered. First, this is an epidemiologic study, a causative link between IE and cancer can’t be established. Secondary, although we tried to use propensity score method to avoid possible confounders, detailed individual information as personal habits, family history, life style, and environmental exposure were not included in claims data. Also, we cannot identify the microorganisms related to IE. Third, certain carcinogenesis may need a longer time for cancer development. Although our study included 10-year follow-up, the follow-up duration could be relative short. Our study provides further investigation between IE and cancer risk.

CONCLUSION

In conclusion, cancer risk, particularly digestive and hematologic malignancies, is substantially increased in IE survivors. The effect remains greater during 10-year follow-up. Our results also provide additional evidence that aspirin use is effective in reducing overall cancer risk in IE survivors.

ACKNOWLEDGMENTS

This study was based in part on data from the NHIRD provided by Bureau of National Health Insurance (BHNI) of the Department of Health and managed by the NHRI. The conclusions presented in this study are those of the authors and do not necessarily reflect the views of the BHNI, the Department of Health, or the National Health Research Institute.

GRANT SUPPORT

None.

REFERENCES

1. Are C, Chowdhury S, Ahmad H, et al. Predictive global trends in the incidence and mortality of pancreatic cancer base on geographic location, socioeconomic status, and demographic shift. J Sung Oncol 2016;114:736-42.
2. Shen X, Wang L, Zhu L. Spatial analysis of regional factors and lung cancer mortality in China, 1973-2013. Cancer Epidemiol Biomarkers Prev 2017;26:569-77.
3. Singer S, Bartels M, Briest S, et al. Socioeconomic disparities in long-term cancer survival:10-year follow-up with individual patient data. Support Care Cancer 2016;25:1391-9.
4. Plummer M, De Martel C, Vignat J, et al. Global burden of cancers attributable to infections in 2012: A synthetic analysis. Lancet Global Health 2016;4:e609-16.
5. Durack D, Lukes A, Bright D. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med 1994;96:200-8.
6. Mesa Del Castillo-Paya C, Rodriguez-Esteban M, Quijada-Fumero A, et al. Infective endocarditis in patients with oncological diseases. Enferm Infecc Microbiol Clin 2016;30:213-5X (16):30344-5.
7. Sharara AI, Abou HT, Malli A, et al. Association of Streptococcus bovis endocarditis and advanced colorectal neoplasma: A casecontrol study. J Dig Dis 2013;14:382-7.
8. Simon MS, Rosenberg CA, Rodalbough RJ, et al. Prospective analysis of association between use of statins or other lipid-lowering agents and colorectal cancer risk. Ann Epidemiol 2012;22:17-27.
9. Friis S, Riis AH, Erichsen R, et al. Low-dose aspirin or nonsteroidal anti-inflammatory drug use and colorectal cancer risk: a population-based, case-control study. Ann Intern Med 2015;163:347-55.
10. Nan H, Hutter CM, Lin Y, et al. Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants. JAMA 2015;313:1133-42.
11. Thomsen RW, Farkas DK, Friis S, et al. Endocarditis and risk of cancer: a Danish nationwide cohort study. Am J Med 2013;126:58-67.
12. Cresti A, Chiavarelli M, Scalese M, et al. Epidemiological and mortality trends in infective endocarditis, A 10-year population-based prospective study. Cardiovase Diagn Ther 2017;7:27-35.
13. Shih CJ, Chu H, Chao PW, et al. Longterm clinical outcome of major adverse cardiac events in survivors of infective endocarditis: A nationwide population-based study. Circulation 2014;130:16849-91.
14. Cheng CL, Kao YH, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 2011;20:2360-4.
15. Heino M, Helenius H, Hurme S, et al. Longterm outcome of infective endocarditis. A study on patients surviving over one year after the initial episode treated in a Finnish teaching hospital during 25 years. BMC Infect Dis 2008;8:49.
16. Chen SJ, Chao TF, Lin YJ, et al. Cool seasons are related to poor prognosis in patients with infective endocarditis. Int J Biometeorol 2012;56:97381.
17. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373-83.
18. Hicks BM, Murray LJ, Hughes C, et al. Clopidogrel use and cancerspecific mortality: A population-based cohort study of colorectal, breast and prostate cancer patients. Pharmacoepidemiol Drug Saf 2015;24:83040.
19. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med 2008;27:2037-49.
20. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
21. Yu TM, Chuang YW, Yu MC, et al. Risk of cancer in patients with polycystic kidney disease: A propensity-score matched analysis of a nationwide cohort study. Lancet Oncol 2016;17:1419-25.
22. Hsiang JC, Wong GL, Tse YK, et al. Statin and the risk of hepatocellular carcinoma and death in a hospital-based hepatitis B-infected population: A propensity score landmark analysis. J Hepatol 2015;63:1190-7.
23. Yanik EL, Kartki HA, Engels EA. Cancer risk among the HIV-infected elderly in the United States. AIDS 2016;30:1663-8.
24. Ishida Y, Aiu D, Maeda M, et al. Secondary cancers after a childhood cancer diagnosis: A nationwide hospital-based retrospective cohort study in Japan. Int J Clin Oncol 2016;21:506-16.
25. Garcia-Albeniz X, Hsu J, Lipsitch M, et al. Infective endocarditis and cancer in the elderly. Eur J Epidemiol 2016;31:419-9.
26. Rothwell PM, Wilson M, Elsin CE, et al. Longterm effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomized trials. Lancet 2010;376:1741-50.
27. Cao Y, Nishihara R, Wu K, et al. Population-wide impact of longterm use of aspirin and the risk for cancer. JAMA oncrol 2016;2,762-9.
28. Zhong S, Chen L, Zhang X, et al. Aspirin use and risk of breast cancer. Systemic review and meta-analysis of observational studies. Cancer Epidemiol Biomarkers Prev 2015;24:1645-55.

29. Lapi F, Levi M, Simonetti M, et al. Risk of prostate cancer in low-dose aspirin users: A retrospective cohort study. Int J Cancer 2016;139:205-11.

30. Eisen DP, Corey GR, McBryde ES, et al. Reduced valve replacement surgery and complication rate in *Staphylococcus aureus* endocarditis patients receiving acetyl-salicylic acid. J Infect 2009;58:332-8.

31. Veloso TR, Oechslin F, Que YA, et al. Aspirin plus ticlopidine prevented experimental endocarditis due to *Enterococcus faecalis* and *Streptococcus gallolyticus*. Pathog Dis 2015;73: ftv060.