Non-Dental Invasive Procedures and Risk of Infective Endocarditis – Time for a Revisit

A Scientific Advisory from the American Heart Association

Larry M. Baddour, MD, FAHA, Chair; Imre Janszky, MD, PhD; Martin H. Thornhill, MBBS, BDS, PhD, Vice Chair; Zerelda Esquer Garrigos, MD; Daniel C. DeSimone, MD; Karen Welty-Wolf, MD; Annette L. Baker, RN, MSN, PNP; Pei-Ni Jone, MD, FAHA;

Bernard Prendergast, BM, BS, MD; Mark J. Dayer, MBBS, PhD; on behalf of the American Heart Association Council on Cardiovascular and Stroke Nursing

Corresponding Author:

Larry Baddour, MD

Mayo Clinic

200 First Street SW

Rochester, Minnesota 55905

UNITED STATES

507-285-3202

baddour.larry@mayo.edu

Abstract

There have been no published prospective randomized clinical trials that have: 1) established an association between invasive dental and non-dental invasive procedures (NDIPs) and risk of infective endocarditis; or 2) defined the efficacy and safety of antibiotic prophylaxis administered in the setting of invasive procedures in the prevention of IE in high-risk patients. Moreover, previous observational studies that examined the association of NDIPs with the risk of IE have been limited by inadequate sample size. They have typically focused on a few potential at-risk surgical and non-surgical invasive procedures. However, recent investigations from Sweden and England that used nationwide databases and demonstrated an association between NDIPs, and the subsequent development of IE (particularly in high-risk IE patients) prompted the development of the current Science Advisory.

Key words: AHA Science Advisory; endocarditis, non-dental invasive procedures, risk antibiotic prophylaxis

Please address all correspondence to: Larry M. Baddour, MD, Mayo Clinic, 200 First Avenue SW, Rochester, MN 55905. Email address: baddour.larry@mayo.edu

Introduction and Overview

Infective endocarditis is associated with a risk of devastating complications, and attempts at its prevention in high-risk individuals are warranted. To date, prevention strategies have focused on invasive dental procedures and resultant transient bloodstream infection due to oral streptococci, and questioned whether antibiotic prophylaxis before dental procedures could reduce the likelihood of IE. No prospective randomized clinical trial has been conducted to determine if there is an association between invasive procedures and the onset of IE and whether antibiotic prophylaxis is effective in IE prevention. Key stakeholders, including the American Heart Association (AHA) and the European Society of Cardiology (ESC), continue to recommend antibiotic prophylaxis in high-risk individuals who undergo invasive dental procedures. Recent extensive case-crossover analyses and cohort studies in large US populations support this notion.[1,2] However, there are no recommendations for a similar approach for non-dental invasive procedures (NDIPs) due to a lack of supporting evidence.

Findings from two recently published nationwide investigations suggest that the link between NDIPs and the risk of IE in high-risk patients (and the potential role of antibiotic prophylaxis) should be revisited. Several NDIPs were strongly associated with the risk of IE in a case-crossover study of >7,000 cases of IE derived from the Swedish National Patient Register,[3] and similar temporal associations were confirmed in

>14,000 English patients with IE.[4] The present Science Advisory further addresses this question in light of the new evidence. The Science Advisory has no role in the interpretation of current guidance from the AHA or other societies but was drafted to highlight an issue that may be considered by subsequent guidelines committees.

Current International Guidelines

American Heart Association (AHA)/American College of Cardiology (ACC) (Table 1)

Despite a lack of clinical trial data supporting a link between invasive procedures and the risk of development of IE, the AHA has endorsed the potential benefit of antibiotic prophylaxis in 10 of the 11 iterations over the past 70 years. In the earliest (1955) document, antibiotic prophylaxis was recommended for patients with rheumatic or congenital heart disease before dental procedures and NDIPs, including removal of tonsils and adenoids, normal vaginal delivery, and surgery on the gastrointestinal or urinary tract.[5] The 1990 version[6] was unique in providing a more detailed description of specific NDIPs where antibiotic prophylaxis should be considered in moderate- and high-IE-risk patients and was followed by similar recommendations in 1997 using more simplified antibiotic regimens.[7]

A *major* shift in perspective came in 2007 (Table 1)[8] in recognition of concerns regarding antimicrobial stewardship, adverse reactions and increasing antibiotic resistance, and the fact that antibiotic prophylaxis would likely prevent only a small number of IE cases. The focus remained on patients at the highest risk of IE complications with weak recommendations for the use of antibiotic prophylaxis before procedures involving established infections of the genitourinary,

gastrointestinal, skin, soft tissue, or musculoskeletal tracts (Class IIb, Level of Evidence B), respiratory tract procedures involving incision or biopsy in high-risk individuals (Class IIa, LOE C), and no use before gastrointestinal and genitourinary procedures (Class III Level of Evidence B). Furthermore, the most recent recommendations focused exclusively on preventing IE due to viridans group streptococci with no mention of NDIPs.[9]

European Society of Cardiology (ESC) Guidelines (Table 1)

Reflecting ACC/AHA guidance, ESC recommendations regarding the use of antibiotic prophylaxis have become progressively more constrained. Thus, while the 2004 ESC guidelines recommended AP for patients at moderate- and high-IE risk undergoing a broad range of both dental and NDIPs,[10] this position was revised in 2009 to match the AHA guidelines restricting antibiotic prophylaxis to patients at high risk undergoing invasive dental procedures[11] – a position that was upheld in the latest ESC guideline recommendations in 2015.[12]

UK Guidelines (Table 1)

The British Society for Antimicrobial Chemotherapy (BSAC) produced guidelines in 2006 that broadly paralleled 2004 ESC recommendations of antibiotic prophylaxis for a wide range of procedures in high-IE-risk patients.[13] The National Institute for Health and Care Excellence (NICE), however, provided new guidance in 2008 that recommended the *complete cessation* of antibiotic prophylaxis for all procedures in all patients. A review in 2015 reaffirmed this guidance, but it was softened one year

later (to: "antibiotic prophylaxis against infective endocarditis is not *routinely* recommended for people undergoing dental procedures") following a change in the UK law on consent.[14] However, NICE provided no guidance as to which situations should be considered "non-routine" or which antibiotic regimens should be used.

Do Invasive Procedures Increase the Risk of Infective Endocarditis? (Tables 2a & 2b)

We identified eight cohort, case-control and case-crossover studies that examined the risk of developing IE after a NDIP in an Embase- and Medline-generated literature-based review done on December 28, 2022 (Supplemental Material).

Lacassin *et al* (1995)[15] In a case-control study "to estimate the relative risk of IE associated with various medical, surgical and dental procedures",[15] Lacassin *et al.* prospectively identified IE cases defined by von Reyn's criteria,[16] and supplementary echocardiographic and histological findings to strengthen diagnostic accuracy. The study included 171 cases and 171 matched control patients recruited from cardiology or medical wards, and all procedures involving cutaneous and mucosal surfaces were recorded. In the adjusted analysis, having a procedure (OR 1.6, [1.01-2.53]) and having a surgical procedure (OR 4.7, [1.02-22]) within three months before the diagnosis of IE or study entry were both associated with the risk of IE. Of note, this study was undertaken when AP was used routinely, and analysis was not stratified according to IE risk.

Strom *et al* 2000[17] In this case-control study, patients with community-acquired IE were compared with community controls matched according to age, sex, and neighborhood of residence; people who inject drugs were excluded. Among 287 selected patients, 273 completed an interview and were compared with 273 controls. After adjustment for socioeconomic factors, pre-existing valve disease, severe renal disease, and diabetes mellitus, only barium enemas were significantly associated with the development of IE (adjusted OR, 11.9 [1.34–106], p=0.026) among a wide variety of NDIPs (including bronchoscopy, lung biopsy, barium enema, upper and lower GI endoscopy [including esophageal dilatation], gynecological surgery, urinary catheterization, cystoscopy, lithotripsy, urinary and prostate surgery, sterilization/vasectomy, cardiac procedures, other surgery, intravenous and nasal-oxygen therapy). Of note, barium enema was frequently done within an IE workup, and colonic cancer/polyps were associated with IE development.

Ammar *et al* 2013[18] A case-control study included 175 adult patients with definite IE, according to modified Duke Criteria, and 175 matched adult controls without IE. They looked for a relationship between several procedures and the development of IE. These included upper respiratory tract procedures, gynecological surgery (n=73 cases, n=72 controls), urinary catheterization, other genitourinary procedures, cardiac catheterization, peripheral intravenous lines, central intravenous lines, and "other procedures". The only procedure associated with an increased risk of IE was the presence of a peripheral venous catheter (OR 2.78 [1.32-5.02]).

Mohee *et al* 2014[19] This single-center case-control study was conducted to determine whether urological procedures were associated with the development of IE

and compared four distinct groups of IE patients (n=384) classified according to the causative bacterial species (enterococci, coagulase-negative staphylococci, *Streptococcus bovis*, oral streptococci) with control cases caused by bacteria of unlikely urological origin. Confounding by factors predisposing to IE was therefore minimal. Among a variety of procedures (including hemodialysis, upper and lower GI procedures, and urological procedures), the multivariable analysis demonstrated that patients undergoing urological procedures were significantly more likely to develop IE due to enterococci (OR 8.56 [3.69-19.85], p<0.001).

Garcia-Albeniz *et al* 2016[20] Patients aged 70-79 years with no history of colorectal cancer, prior colectomy, or IE were derived from a random sample (20%) of Medicare beneficiaries in this cohort study, specifically addressing the risk of developing IE after colonoscopy. The authors compared the 3-month IE risk between individuals who underwent colonoscopy for screening, surveillance, or diagnostic purposes versus those who did not after standardizing for several potential confounders, including comorbidities. They further classified individuals with a history of valve disorders, structural heart disease, intra-vascular devices, or end-stage renal disease as "high-risk". Importantly, this definition is inconsistent with "guidelines" criteria for high-IE risk and is more consistent with moderate-IE risk. There were 1,013 IE cases in the symptomatic population (n=994,971), 179 in the surveillance population (n=721,881), and 279 in the prevention population (n=1,462,360). The investigators concluded that the risk of developing IE after colonoscopy was increased in individuals with IE risk factors and GI symptoms but acknowledged that it remained unclear whether colonoscopy or the colonic lesion was responsible for this association.

Sun *et al* 2017[21]

All children born with congenital heart disease in Taiwan between 1997 and 2005 (diagnosed before three years of age) were followed until 2010. IE diagnosis or death and invasive cardiovascular procedures performed during the six months before this index date were identified using the National Health Research Institutes of Taiwan database. Among 24,729 children with congenital heart disease, 273 were newly diagnosed with IE (overall incidence 111.3 per 100,000 person-years), with the highest risk in those undergoing cardiovascular procedures and central venous catheter insertion.

Janszky *et al* 2018[3]

In this case-crossover study, patients aged > 20 years who received in-patient treatment for IE between 1998 and 2011 were identified in the Swedish National Patient Register, and those who had undergone procedures that might be confounded with IE (such as central venous or arterial catheter insertion) were excluded. Case and control periods were defined as 0-84 days and 365-449 days before admission. An inpatient or outpatient invasive procedure was more likely in the 7013 patients with IE during the case period (12 weeks) before developing IE than during the control period a year before. Therapeutic procedures involving the skin, blood transfusion and various operations, and diagnostic procedures (bone marrow puncture, coronary angiography, and some modes of endoscopy [especially bronchoscopy]) were associated the highest risk of IE in the subsequent three months, and risk differences were much greater in those at high IE-risk.

Thornhill *et al* 2022[4]

National admissions data included 14,731 cases of IE identified between 2010 and 2016 in England and all invasive procedures performed on these individuals in the 15 months before admission. The incidence of invasive procedures during the three months immediately before IE admission (case period) was compared with the incidence during the preceding 12 months (control period) to determine whether the odds of developing IE were increased within three months of an invasive procedure. Two analytic techniques – a "step" and a "hinge" model – were employed, the latter correcting for a general increase in the number of procedures over time. The odds of developing IE were significantly elevated after several procedures, including cardiac implantable electronic device procedures, upper and lower GI endoscopy, bone marrow biopsy, blood transfusion, and bronchoscopy. The study also demonstrated that the increased IE risk attributable to these procedures was much greater in subjects at high-IE risk (Figure 1).

Limitations of these studies include a lack of data concerning causative microorganisms and whether AP was given (or not). We also recognize that some of these studies included non-contemporary data and that the selection of controls is always imperfect. Finally, it should be noted that some of these investigations may be temporally linked with the diagnosis of IE but not its cause. For example, endoscopy is commonly used as part of the diagnostic work-up for anemia, but it may be that anemia is secondary to IE, or a reflection of underlying diseases (such as colorectal cancer) that predisposes to IE. Similarly, while the presence of a CIED increases the risk of IE, it may not be the

procedure of CIED implantation that causes IE. Until these limitations are surmounted, it will be difficult to draw definitive conclusions regarding IE causality.

Current Position

Eight studies that included a cohort (1), case-control (5) or case-crossover design(2) evaluated non-dental procedures and the associated risk of IE and were reviewed in this Science Advisory (Tables 2a&b).[3,4,17-22] The results from two of them[3,4] were key in prompting a call for this Science Advisory and deserve further highlighting. Both utilized a case-crossover design which enhanced the control of potential confounders and comorbidities that were stable over time. In addition, both investigations included nationwide cohorts, which eliminated concerns about adequate cohort size for statistical evaluation, and mandatory registration of admissions and invasive procedures prevented bias due to self-selection and biased recall which are important limitations in case-control studies. Both evaluated an extensive list of healthcare-related procedures. Patients labelled as high-risk of IE were at increased risk of developing IE after several non-dental invasive procedures, including CIED implantation, gastrointestinal endoscopy, and bronchoscopy (Figure 1). There are limitations to both the Janszky and Thornhill publications. The indications for invasive procedures and the effect of these procedures were not able to be separated in these studies which might have introduced spurious associations. However, investigators made substantial efforts to exclude the likelihood of procedures being performed as part of the diagnosis or management of IE in the analyses. For example, all procedures were excluded if performed during an IE-related hospital admission and before an IE diagnosis. Procedures associated with attempts to

diagnose IE, for example, transesophageal echocardiogram (TEE) (and some other procedures), were excluded whenever they occurred (including in the weeks/months before an IE-related admission to hospital). There was a strong association between TEE performed in the three months before an IE admission and the subsequent development of IE. This could arguably represent a true association with subsequent IE development. In addition, procedures performed after an IE diagnosis was made but were done for IE management were also excluded. Electronic health records were not available for review, and diagnoses were based on ICD coding. Moreover, there was no information about the use of antibiotics as prophylaxis or treatment to prevent IE.

These latter two limitations may have led to an underestimation of effects. A lack of available microbiologic data in both investigations was also an important shortcoming. This would help validate an association between procedure and development of IE, based on the well-recognized distribution of organisms as unique colonizers of various anatomical locations.

The remaining six studies (Tables 2a & b) deserve comment. In contrast to the publications mentioned above that examined numerous NDIPs, one investigation[20] focused only on colonoscopy and the risk of IE. It included a large population of Medicare beneficiaries; 1471 patients had IE. Based on their definition of patients with "high IE-risk" (history of valve disorders, structural heart disorders, intravenous devices, or end-stage renal disease), there was an increased risk of IE in the high IE-risk patients who underwent a polypectomy or a biopsy during colonoscopy in the setting of recent gastrointestinal symptoms.

Mohee and colleagues[19] focused only on urological procedures that included 384 patients with IE. They demonstrated an association between a procedure and the development of IE due to enterococcal species. Whether the procedure or the underlying urological disorder was responsible for the IE episode was not determined. The population-based case-control study by Strom and colleagues[17] also suffered from limitations. The number of cases and controls for evaluation of individual procedures was too small to secure an appropriate analysis of their risk in predisposing to IE development. This was also the problem with both the Lacassin and the Ammar studies.[15,18]

Future Considerations

The novel evidence assessed in this Science Advisory suggests that the role of NDIPs as risk factors associated with the subsequent development of IE, particularly in those at high-IE risk, should be re-evaluated. The new data indicate that certain invasive medical/surgical procedures have the potential to cause IE, particularly in those at high-IE risk. These findings have at least two potential implications in clinical practice. First, there is a need to educate clinicians performing these procedures on the potential risk posed by them in high IE-risk patients. This would include scrupulous attention to sterility and infection prevention and control interventions normally undertaken with these procedures. For procedures that involve repeated or long-term insertion of transcutaneous catheters, e.g., hemodialysis, insertion of central venous catheters etc., scrupulous sterility and infection prevention and control precautions are likely to be

particularly important in reducing the risk that they pose to high IE-risk patients; the repeated or long-term use of antibiotics to reduce the risk of IE associated with these procedures is impractical and has been associated with the promotion of antibiotic resistance among colonizing strains. For procedures where antibiotics are routinely prescribed to prevent post-operative surgical site infections, e.g., insertion of CIEDs, ERCPs, trans-urethral and trans-rectal prostate procedures, etc., compliance with post-operative infection prevention and control guidelines, and consideration of antibiotic regimens that might also help to prevent IE, may be particularly important in individuals at high IE-risk. Indeed, there may be reason to consider using augmented or supplemental methods to prevent surgical site infections in this group of patients, e.g., using an antibiotic-impregnated envelope to prevent CIED infections.[23]

For NDIPs, where there may be a significantly increased risk of IE in those at high IE-risk, but currently there are no specific post-operative infection prevention guidelines, e.g., most endoscopy procedures, it may be appropriate to consider if there are specific actions that could be taken to reduce the IE-risk in high-risk patients. Guidelines committees may wish to consider if individuals at high IE risk undergoing NDIPs would benefit from AP regimens targeted against typical colonizing bacteria.

Second, there is a need to educate and alert primary and secondary care physicians to the possibility of IE occurring in high IE-risk individuals in whom NDIPs have recently been performed (particularly in the preceding three months). This alertness is important to ensure the earliest possible diagnosis and treatment of IE in high-risk individuals to obtain optimal treatment outcomes.

Because randomized clinical trials have not been feasible, largely due to the low incidence of IE, high-quality large observational studies are essential to help validate further advice and guidance, particularly related to high-risk procedures and high IE-risk patients.

In summary, we propose that there is sufficient evidence associating certain NDIPs with the subsequent occurrence of IE, particularly in those at high IE risk, to warrant a re- evaluation of IE prevention advice.

Acknowledgments The writing group thanks Danielle J. Gerberi, MLS, AHIP, for her expert assistance in performing the literature search.

References

1. Thornhill MH, Gibson TB, Yoon F, Dayer MJ, Prendergast BD, Lockhart PB, O'Gara PT, Baddour LM. Antibiotic Prophylaxis Against Infective Endocarditis Before Invasive Dental Procedures. *J Am Coll Cardiol*. 2022;80:1029-1041. doi: 10.1016/j.jacc.2022.06.030
2. Thornhill MH, Gibson TB, Yoon F, Dayer MJ, Prendergast BD, Lockhart PB, O'Gara PT, Baddour LM. Endocarditis, invasive dental procedures, and antibiotic prophylaxis efficacy in US Medicaid patients. Oral Diseases. 2023 Apr 27. doi: 10.1111/odi.14585.;
3. Janszky I, Gemes K, Ahnve S, Asgeirsson H, Moller J. Invasive Procedures Associated With the Development of Infective Endocarditis. *J*

Am Coll Cardiol. 2018;71:2744-2752. doi: https://dx.doi.org/10.1016/j.jacc.2018.03.532

4. Thornhill MH, Crum A, Campbell R, Stone T, Lee EC, Bradburn M, Fibisan V, Dayer M, Prendergast BD, Lockhart P, Baddour L, Nicoll J. Temporal association between invasive procedures and infective endocarditis. *Heart*. 2022;22:22. doi: https://dx.doi.org/10.1136/heartjnl-2022-321519
5. Jones TD, Baumgartner L, Bellows MT, Breese BB, Kuttner GG, McCarty M, Rammelkamp CH. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. *Circulation*. 1955;11:317-320.
6. Dajani AS, Bisno AL, Chung KJ, Durack DT, Freed M, Gerber MA, Karchmer AW, Millard HD, Rahimtoola S, Shulman ST, Watanakunakorn C, Taubert KA. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *Jama*. 1990;264:2919-2922.
7. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, Gewitz MH, Shulman ST, Nouri S, Newburger JW, Hutto C, Pallasch TJ, Gage TW, Levison ME, Peter G, Zuccaro G. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *Circulation*. 1997;96:358-366. doi: 10.1161/01.cir.96.1.358
8. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, Newburger JW, Strom BL, Tani LY, Gerber M, Bonow RO, Pallasch, Shulman ST, Rowley AH, Burns JC, Ferrieri P, Gardner T, Goff D, Durack DT. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the

Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736- 1754. doi: 10.1161/CIRCULATIONAHA.106.183095

9. Wilson WR, Gewitz M, Lockhart PB, Bolger AF, Desimone DC, Kazi DS, Couper DJ, Beaton A, Kilmartin C, Miro JM, Sable C, Jackson MA, Baddour LM. Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement from the American Heart Association. *Circulation*. 2021;143(20):E963-E978. doi: https://dx.doi.org/10.1161/CIR.0000000000000969

10. Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, Soler-Soler J, Thiene G, von Graevenitz A, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Deckers DV, Fernandez BE, Lekalis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth QA, Kekakis J, Vahanian A, Delahaye F, Parkhomenko A, Filipatos G, Aldershvile J, Vardas P. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary; the task force on infective endocarditis of the European society of cardiology. *Eur Heart J*. 2004;25:267-276. doi: 10.1016/j.ehj.2003.11.008

11. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Muller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL. Guidelines on the prevention, diagnosis,

and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of

Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J*. 2009;30:2369-2413. doi: 10.1093/eurheartj/ehp285

12. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, et Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075-3128. doi: 10.1093/eurheartj/ehv319
13. Gould FK, Elliott TS, Foweraker J, Fulford M, Perry JD, Roberts GJ, Sandoe JA, Watkin RW, Working Party of the British Society for Antimicrobial C. Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2006;57:1035-1042. doi: 10.1093/jac/dkl121
14. NICE Clinical Guideline 64. Prophylaxis against infective endocarditis: Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. National Institute for Health and Care Excellence; 2008. Updated 2015. Amended 2016; Accessed 21/03/2023. https://www.nice.org.uk/guidance/cg64/evidence/full-guideline-pdf-196759981
15. Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V, Etienne J, Briancon S. Procedures associated with infective endocarditis in adults. A case control study. *Eur Heart J*. 1995;16:1968-1974. doi:

10.1093/oxfordjournals.eurheartj.a060855

16. von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. *Ann Intern Med*. 1981;94:505-518. doi: 10.7326/0003-4819-94-4-505

17. Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, Levison ME, Korzeniowski OM, Kaye D. Risk factors for infective endocarditis: oral hygiene and nondental exposures. *Circulation*. 2000;102:2842-2848. doi: 10.1161/01.cir.102.23.2842

18. Ammar W, El AW, El MA. Case-control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care center. *Egyptian Heart Journal*. 2013;65:153-157.

19. Mohee AR, West R, Baig W, Eardley I, Sandoe JA. A case-control study: are urological procedures risk factors for the development of infective endocarditis? *BJU Int*. 2014;114:118-124. doi: 10.1111/bju.12550

20. Garcia-Albeniz X, Hsu J, Lipsitch M, Bretthauer M, Logan RW, Hernandez-Diaz S, Hernan MA. Colonoscopy and Risk of Infective Endocarditis in the Elderly. *J Am Coll Cardiol*. 2016;68:570-571. doi: https://dx.doi.org/10.1016/j.jacc.2016.05.041

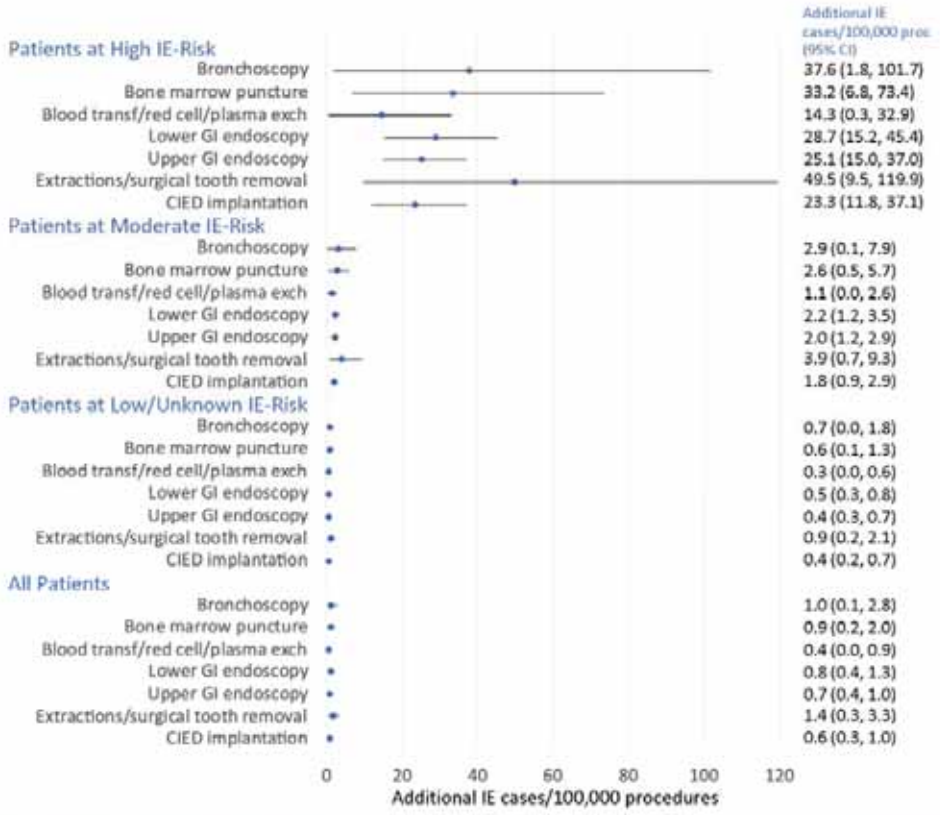
21. Sun LC, Lai CC, Wang CY, Wang YH, Wang JY, Hsu YL, Hu YL, Wu ET, Lin MT, Sy LB, Chen L. Risk factors for infective endocarditis in children with congenital heart diseases - A nationwide population-based case control study. *Int J Cardiol*. 2017;248:126-130. doi: 10.1016/j.ijcard.2017.08.009

22. Standards for Implantation and Follow-up of Cardiac Rhythm Management Devices in Adults. January 2018 revision. British Heart Rhythm Society. 2023https://bhrs.com/wp-content/uploads/2019/10/BHRS-standards-January-

2018- Implantation-and-Follow-Up-of-CRM-Devices-in-Adults.pdf. Accessed February 28, 2023.

23. Tarakji KG, Mittal S, Kennergren C, Corey R, Poole JE, Schloss E, Gallastegui J, Pickett RA, Evonich R, Philippon F, McComb JM Roark SF, Sorrentino D, Sholevar D, Cronin E, Berman B, Riggio D, Biffi M, Khan H, Silver MT, Collier J, Eldadah Z, Wright DJ, Lande JD, Lexcen DR, Cheng A, Wilkoff BL, for the WRAP-IT Investigators . Antibacterial Envelope to Prevent Cardiac Implantable Device Infection. *N Engl J Med*. 2019;380:1895-1905. doi: 10.1056/NEJMoa1901111

24. Leport C, Horstkotte D, Burckhardt D. Antibiotic prophylaxis for infective endocarditis from an international group of experts towards a European consensus. Group of Experts of the International Society for Chemotherapy. *Eur Heart J*. 1995;16 Suppl B:126-131. doi: 10.1093/eurheartj/16.suppl_b.126



Notes: The attributable risk (or absolute risk increase) is presented for IPs with a significant positive temporal association with subsequent IE and is expressed as the additional number of IE cases per 100,000 procedures. The population at risk was estimated using the population of England during the middle year of the study (2012-23) and estimates for the proportion of the population at high, moderate or low/unknown risk. Baseline risk was calculated as the average three-monthly risk of being subject to each procedure for each population over the study period (March 2010 to December 2015, excluding the last 3 months of data). The attributable risk was calculated by multiplying the baseline risk with the adjusted OR estimate from Table 3. GI = gastrointestinal, IPs = invasive procedures, transf = transfusion, exch = exchange.

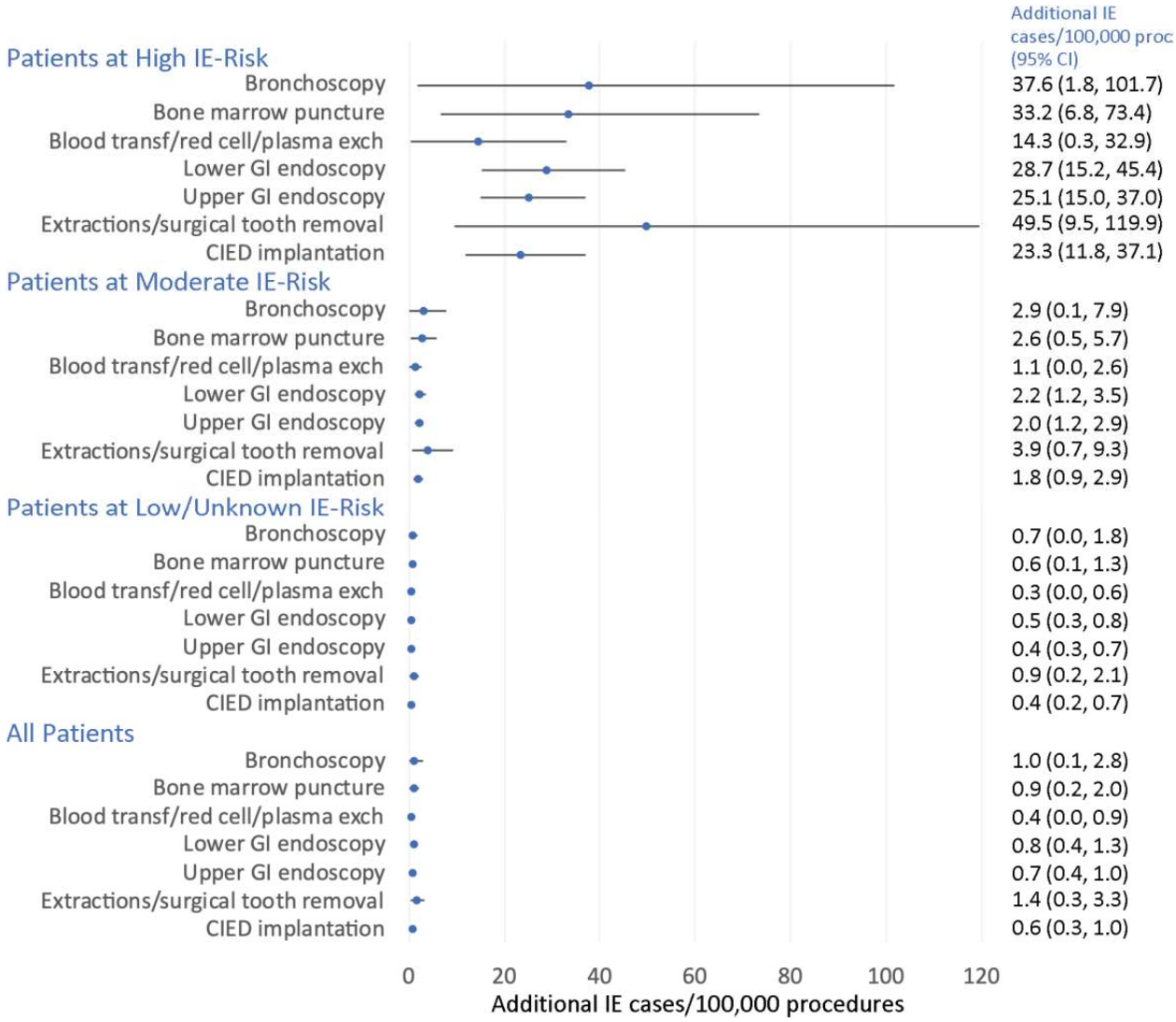

Additional IE cases/100,000 proc (95% CI)
Patients at High IE-Risk
Bronchoscopy
37.6 (1.8, 101.7)
Bone marrow puncture
33.2 (6.8, 73.4)
Blood transf/red cell/plasma exch
14.3 (0.3, 32.9)
Lower GI endoscopy
28.7 (15.2, 45.4)
Upper GI endoscopy
25.1 (15.0, 37.0)
Extractions/surgical tooth removal
49.5 (9.5, 119.9)
CIED implantation
23.3 (11.8, 37.1)
Patients at Moderate IE-Risk
Bronchoscopy
2.9 (0.1, 7.9)
Bone marrow puncture
2.6 (0.5, 5.7)
Blood transf/red cell/plasma exch
1.1 (0.0, 2.6)
Lower GI endoscopy
2.2 (1.2, 3.5)
Upper GI endoscopy
2.0 (1.2, 2.9)
Extractions/surgical tooth removal
3.9 (0.7, 9.3)
CIED implantation
1.8 (0.9, 2.9)
Patients at Low/Unknown IE-Risk
Bronchoscopy
0.7 (0.0, 1.8)
Bone marrow puncture
0.6 (0.1, 1.3)
Blood transf/red cell/plasma exch
0.3 (0.0, 0.6)
Lower GI endoscopy
0.5 (0.3, 0.8)
Upper GI endoscopy
0.4 (0.3, 0.7)
Extractions/surgical tooth removal
0.9 (0.2, 2.1)
CIED implantation
0.4 (0.2, 0.7)
All Patients
Bronchoscopy
1.0 (0.1, 2.8)
Bone marrow puncture
0.9 (0.2, 2.0)
Blood transf/red cell/plasma exch
0.4 (0.0, 0.9)
Lower GI endoscopy
0.8 (0.4, 1.3)
Upper GI endoscopy
0.7 (0.4, 1.0)
Extractions/surgical tooth removal
1.4 (0.3, 3.3)
CIED implantation
0.6 (0.3, 1.0)
0
20
40
60
80
100
120
Additional IE cases/100,000 procedures

Figure Legend

Figure 1. Attributable risk – the predicted additional IE cases per 100 000 procedures by patient risk group. The attributable risk is presented for IPS with a significant positive temporal association with subsequent IE and is expressed as the predicted additional number of IE cases per 100 000 procedures. The population at risk was estimated using the population of England during the middle year of the study (2012–2023) and estimates for the proportion of the population at high, moderate or low/unknown risk. Baseline risk was calculated as the average 3 monthly risk of being subject to each procedure for each population over the study period (March 2010–December 2015, excluding the last 3 months of data). The attributable risk was calculated by multiplying the baseline risk with the adjusted or estimate from table 1. CIED, cardiac implantable electronic devises; exch, exchange; GI, gastrointestinal; IE, infective endocarditis; IPS, invasive procedures; transf, transfusion.

Table 1. Recommendations for the use of antibiotic prophylaxis prior to invasive procedures in previous guidelines

Guidelines/Recommendations	**AHA 1990[14]**	**AHA 1997[7]**	**AHA 2007[8]**	**AHA 2021[9]**	**ESC 1995[24]**	**ESC 2004[10]**	**ESC 2009[11]/15[12]**	**UK – BSAC 2006[13]**	**UK – NICE 2008/2015/2016[11]**
Risk groups where AP recommended	Moderate & high risk	Moderate & high risk	High risk only	High risk only	Moderate & high risk	Moderate & high risk	High risk only	Moderate & high risk	None
Invasive Procedures									
GI Procedures							[c]		
GI endoscopy with/without biopsy	✓†	✓†	-	-	✓[b]	-	-	✓*	-
Esophageal dilatation/sclerotherapy	✓	✓#	-	-	✓	✓	-	✓	-
Endoscopic retrograde cholangio-pancreatography or biliary surgery	✓	✓#	-	-	-	✓	-	✓	-
GI Surgery	✓	✓#	-	-	✓	-	-	✓	-
GU Procedures							[c]		
Endoscopic prostate procedures / prostate surgery	✓	✓	-	-	✓	✓	-	✓	-
Cystoscopic and endoscopic urological procedures	✓	✓	-	-	✓	✓§	-	✓	-
Urinary tract catheterization or surgery	✓§	✓§	-	-	✓	✓	-	-	-
Obstetric & Gynecological Procedures									
Caesarean section	-	-	-	-	-	✓§	-	✓	-
Vaginal delivery	✓§	✓†	-	-	✓§	✓§	-	✓§	-
Abortion/dilatation and curettage	✓§	✓§	-	-	-	✓§	-	✓§	-
Vaginal hysterectomy	✓	✓†	-	-	✓§	✓§	-	✓	-
Insertion/removal of intrauterine devices or sterilization procedures	✓§	✓§	-	-		✓§	-	✓§	-
Respiratory Procedures							[c]		
Bronchoscopy - rigid	✓	✓	-[a]	-	-	✓	-	-	-
Bronchoscopy - flexible	✓†	✓†	-[a]	-	✓[b]	-	-	-	-
Endotracheal intubation	-	-	-	-	✓[b]	-	-	-	-
Surgery involving respiratory mucosa	✓	✓	✓		-	-	-	✓	-
Cardiac Procedures									
Implantation of pacemakers/defibrillators	-	-	-	-	-	-	-	-	-

Percutaneous valve procedures	-	-	-	-	-	-	-	-	-
Percutaneous coronary procedures/stents	-	-	-	-	-	-	-	-	-
Coronary artery bypass grafting	-	-	-	-	-	-	-	-	-
Coronary angiography	-	-	-	-	-	-	-	-	-
ENT Procedures									
Tonsillectomy/adenoidectomy	✓	✓	✓	-	✓	✓	-	✓	-
Nasal packing/nasal intubation	-	-	-	-	-	-	-	✓	-
Dermatological Procedures							[c]		
Skin suturing, drainage, or wound management	-	-	✓§	-	-	-	-	-	-
Dental Procedures									
Dental extractions	✓	✓	✓	✓	✓	✓	✓	✓*	-
Other oral surgical procedures	✓	✓	✓	✓	✓	✓	✓	✓*	-
Scaling of teeth	✓	✓	✓	✓	✓	✓	✓	✓*	-
Endodontic treatment	✓	✓	✓	✓	✓	✓	✓	✓*	-

Notes: This table summarizes international guideline recommendations over the past 30 years for the use of antibiotic prophylaxis (AP) prior to invasive procedures in those at moderate or high risk of infective endocarditis.

✓ = antibiotic prophylaxis recommended

✓† = antibiotic prophylaxis recommended as optional for high-risk patients

✓# = antibiotic prophylaxis recommended for high-risk patients, optional for moderate-risk

✓§ = antibiotic prophylaxis recommended in the presence of infection

✓* = antibiotic prophylaxis recommended only for those at high-risk
[a] = prophylaxis only recommended if the procedure involves incision of respiratory mucosa

✓[b] = antibiotic prophylaxis recommendation considered controversial
[c] = antibiotic prophylaxis only for consideration in high-risk patients undergoing procedures to treat an established infection or where antibiotic therapy is indicated to prevent wound infection or sepsis

Abbreviations: AHA = American Heart Association, AP = antibiotic prophylaxis, BSAC = British Society for Antimicrobial Chemotherapy, ENT = ear, nose and throat, ESC = European Society for Cardiology, GI = gastrointestinal, GU = genitourinary, UK = United Kingdom, NICE = National Institute for Health and Care Excellence.

Table 2a. Comparison of Case-Control and Case-Crossover Studies

Study	**Lacassin[15]**	**Strom[17]**	**Ammar[18]**	**Mohee[19]**	**Garcia-Albeniz[20]**
Year	**1995**	**2000**	**2013**	**2014**	**2016**
Subgroup	N/A	N/A	N/A	N/A	N/A
Study type	Case control	Case control	Case control	Case control	Cohort
Measure of association	OR (95% CI, p value)	OR (95% CI, p value)	OR (95% CI, p value)	OR (95%CI, p value)	RD
Adjusted/unadjusted	Adjusted	Adjusted	Unadjusted	Adjusted	N/A
Risk period studied	3 months	3 months	3 months	1 year	3 months
Population	Ile de France, Rhone-Alpes, Lorraine	54 hospitals in Philadelphia and Delaware	Cairo University Hospital	Leeds Teaching Hospitals NHS Trust	20% Medicare sample
Dates	1/11/1990-31/10/1991	08/1988-11/1990	03/2005-06/2008	01/01/2001-31/12/2010	1999-2012
Patients with endocarditis, n	171	273	175	384	1,471
Controls, n	171	273	175	-	3,177,741
GI Procedures					
Any GI procedure	1.7 (0.7-4.1, ns)	-	-	-	-
Barium enema	-	11.9 (1.34-106, 0.03)	-	-	-
Upper GI endoscopy with/without biopsy	-	1.36 (0.26-6.99, 0.71)	-	-	-
Lower GI endoscopy with/without biopsy	-	1.95 (0.58-6.53, 0.28)	-	-	-
Colonoscopy with biopsy / polypectomy	-	-	-	-	Excess 7.3 cases of IE / 10,000 vs. no colonoscopy in "high risk" patients
Colonoscopy	-	-	-	-	-
Sigmoidoscopy	-	-	-	-	-
Rectoscopy	-	-	-	-	-
Endoscopic retrograde cholangio-pancreatography) / biliary surgery	-	-	-	-	-
Other diagnostic transluminal endoscopy (upper or lower GI), oropharyngoscopy, ureteroscopy	-	-	-	-	-
Therapeutic transluminal GI endoscopic procedures	-	-	-	-	-
Colonic surgery	-	-	-	-	-
GU Procedures					
Any urological procedure	3.1 (0.6-15.7, ns)	-	-	-	-
Any urological procedure (excluding catheterization)	-	0.61 (0.06-5.80, 0.67)	3.02 (0.12-74.58, 0.50)	-	-
Endoscopic prostate procedures / prostate surgery	-	-	-	-	-
Any transurethral endoscopic procedure (excluding catheterization)	-	-	-	8.21 (3.54-19.05, <0.001)	-

Cystoscopy	-	-	-	-	-
Urinary catheterization	-	0.58 (0.11-4.10, 0.52)	0.33 (0.06-1.64, 0.17)	-	-
Obstetric & Gynecological Procedures					
Caesarean section	-	-	-	-	-
Vaginal delivery	-	-	-	-	-
Abortion/dilatation and curettage	-	-	-	-	-
Gynecological surgery	-	-	0.25 (0.03-2.22, 0.21)	-	-
Respiratory Procedures					
Any respiratory procedure	-	0.27 (0.01-5.46, 0.39)	0.20 (0.01-4.15, 0.30)	-	-
Bronchoscopy (flexible or rigid)	-	-	-	-	-
Cardiac Procedures					
Implantation of pacemakers/defibrillators	-	-	-	-	-
Percutaneous valve procedures	-	-	-	-	-
Percutaneous coronary intervention	-	-	-	-	-
Coronary artery bypass graft	-	-	-	-	-
Coronary angiography	-	-	0.75 (0.16-3.38, 0.70)	-	-
Implantation of pacemaker or defibrillator, surgery of aorta and large arteries, open heart surgery, or minor cardiac surgery	-	-	-	-	-
Open heart surgery	-	-	-	-	-
Valve surgery	-	-	-	-	-
Shunt surgery	-	-	-	-	-
ENT Procedures					
Tonsillectomy/adenoidectomy	-	-	-	-	-
Therapeutic ENT procedures	-	-	-	-	-
Nasal packing/intubation	-	-	-	-	-
Dermatological Procedures					
Skin suturing, drainage, or wound management	-	-	-	-	-
Hematological Procedures					
Blood transfusion/red cell/plasma exchange	-	-	-	-	-
Bone marrow puncture	-	-	-	-	-
Surgical Procedures					
Any surgical procedure	4.7 (1.02-22, <0.05)	-	-	-	-
Other surgery (not cardiac)	-	0.49 (0.12-2.11, 0.34)	2.01 (0.18-22.39, 0.57)	-	-
Other surgery (not cardiac, but including electrophysiology studies)	-	-	-	-	-
Any/Other Procedure					

Arterial puncture	-	-	-	-	-
Intravenous therapy	-	1.16 (0.38-3.57, 0.79)	-	-	-
Peripheral intravenous line	-	-	2.78 (1.32-5.02, 0.005)	-	-
Central intravenous line	-	-	2.02 (0.37-11.19, 0.42)	-	-
Nasal oxygen therapy	-	6.15 (0.78-48.8, 0.09)	-	-	-
Prior hospitalization	-	-	4.2 (2.5-7.02, <0.001)	-	-
Rhinopharyngoscopy, laryngoscopy, esophagoscopy, hysteroscopy	-	-	-	-	-
Genitourinary and obstetric procedures	-	-	-	-	-
Any procedure	1.6 (1.01-2.53, <0.05)	-	-	-	-

Abbreviations: ENT = ear, nose and throat, GI = gastrointestinal, GU = genitourinary, OR = odds ratio, RD= risk difference.

Table 2b. Comparison of Case-Control and Case-Crossover Studies

Study	**Sun[21]**	**Janszky[3]**	**Janszky[3]**	**Thornhill[4]**	**Thornhill[4]**
Year	**2017**	**2018**	**2018**	**2022**	**2022**
Subgroup	N/A	Inpatient IPs	Outpatient IPs	Step model	Hinge model
Study type	Nested case control	Case crossover	Case crossover	Case crossover	Case crossover
Measure of association	OR (95% CI, p value)	OR (95% CI)	OR (95% CI)	OR (95%CI, p value)	OR (95%CI, p value)
Adjusted/unadjusted	Adjusted	N/A	N/A	N/A	N/A
Risk period studied	6 months	12 weeks	12 weeks	3 months	3 months
Population	Children in Taiwan born between 1997-2005 with congenital heart disease	Sweden	Sweden	England	England
Dates	1997-2010	01/01/1998-31/12/2011	01/01/2001-31/12/2011	01/04/2010-31/03/2016	01/04/2010-31/03/2016
Patients with endocarditis, n	237	7,013	7,013	14,731	14,731
Controls, n	24,492	N/A	N/A	N/A	N/A
GI Procedures					
Any GI procedure	-	-	-	-	-
Barium enema	-	-	-	-	-
Upper GI endoscopy with/without biopsy	-	3.97 (2.68-5.88)	2.50 (1.59-3.94)	1.58 (1.34-1.85, <0.001)	1.30 (1.22-1.39, <0.001)
Lower GI endoscopy with/without biopsy	-	-	-	1.66 (1.35-2.04, <0.001)	1.23 (1.13-1.34, <0.001)
Colonoscopy with biopsy/polypectomy	-	-	-	-	-
Colonoscopy	-	2.82 (1.42-5.61)	2.89 (1.35-6.17)	-	-
Sigmoidoscopy	-	2.17 (0.82-5.70)		-	-
Rectoscopy	-	2.67 (1.04-6.82)		-	-
Endoscopic retrograde cholangio-pancreatography) / biliary surgery	-	-	-	0.94 (0.46-1.89, ns)	0.78 (0.57-1.06, ns)
Other diagnostic transluminal endoscopy (upper or lower GI), oropharyngoscopy, ureteroscopy	-	-	2.60 (1.25-5.39)	-	-
Therapeutic transluminal GI endoscopic procedures	-	2.91 (1.77-4.77)	3.33 (0.92-12.11)	-	-
Colonic surgery	-	-	-	1.48 (0.74-2.95, ns)	1.01 (0.76-1.35, ns)
GU Procedures					
Any urological procedure	-	-	-	-	-
Any urological procedure (excluding catheterization)	-	-	-	-	-
Endoscopic prostate procedures / prostate surgery	-	-	-	0.55 (0.33-0.92, ns)	0.72 (0.57-0.91, ns)
Any transurethral endoscopic procedure (excluding catheterization)	-	-	-	0.92 (0.70-1.20, ns)	0.94 (0.83-1.05, ns)

Cystoscopy	-	4.40 (1.67-11.62)	1.59 (0.98-2.58)	-	-
Urinary catheterization	-	-	-	-	-
Obstetric & Gynecological Procedures					
Caesarean section	-	-	-	0.71 (0.10-5.24, ns)	1.28 (0.56-2.94, ns)
Vaginal delivery	-	-	-	0.96 (0.31-2.98, ns)	1.34 (0.83-2.15, ns)
Abortion/dilatation and curettage	-	-	-	1.69 (0.29-9.72, ns)	2.07 (0.99-4.33, ns)
Gynecological surgery	-	-	-	-	-
Respiratory Procedures					
Any respiratory procedure	-	-	-	-	-
Bronchoscopy (flexible or rigid)	-	16.00 (2.12-120.65)	5.00 (1.10-22.82)	1.87 (1.04-3.34, ns)	1.33 (1.06-1.68, 0.049)
Cardiac Procedures					
Implantation of pacemakers/defibrillators	-		-	1.54 (1.27-1.85, <0.001)	1.29 (1.19-1.39, <0.001)
Percutaneous valve procedures	-	-	-	2.57 (0.78-8.45, ns)	1.61 (0.99-2.60, ns)
Percutaneous coronary intervention	-	3.50 (1.41-8.67)	-	1.59 (0.94-2.68, ns)	1.28 (1.03-1.58, ns)
Coronary artery bypass graft	-	13.8 (5.57-34.21)	-	2.99 (0.75-11.96, ns)	1.62 (0.96-2.73, ns)
Coronary angiography	3.74 (2.67-5.22, <0.001)	4.23 (2.93-6.11)	4.75 (1.61-13.96)	1.05 (0.88-1.25, ns)	1.04 (0.97-1.12, ns)
Implantation of pacemaker or defibrillator, surgery of aorta and large arteries, open heart surgery, minor cardiac surgery	-	9.75 (3.48-27.28)	-	-	-
Open heart surgery	2.47 (1.61-3.77, <0.001)	-	-	-	-
Valve surgery	3.20 (1.70-6.02, <0.001)	-	-	-	-
Shunt surgery	7.43 (2.36-23.41, <0.001)	-	-	-	-
ENT Procedures					
Tonsillectomy/adenoidectomy	-	-	-	0.28 (0.03-2.39, ns)	0.58 (0.21-1.56, ns)
Therapeutic ENT procedures	-	2.33 (0.60-9.02)	-	-	-
Nasal packing/nasal intubation	-	-	-	0.71 (0.35-1.44, ns)	0.99 (0.73-1.33, ns)
Dermatological Procedures					
Skin suturing, drainage, or wound management	-	7.00 (0.86-56.89)	-	0.92 (0.67-1.27, ns)	0.96 (0.84-1.10, ns)
Hematological Procedures					
Blood transfusion/red cell/plasma exchange	-	6.69 (4.43-10.11)	5.50 (1.22-24.80)	1.33 (1.01-1.76, ns)	1.20 (1.07-1.35, 0.012)
Bone marrow puncture	-	4.67 (1.34-16.24)	4.33 (1.24-15.21)	1.76 (1.16-2.69, 0.039)	1.28 (1.08-1.52, 0.018)
Surgical Procedures					
Any surgical procedure	-	-	-	-	-
Other surgery (not cardiac)	-	-	-	-	-
Other surgery (not cardiac, but including electrophysiology studies)	-	2.82 (1.73–4.58)	1.49 (1.17-1.90)	-	-
Any/Other Procedure					
Arterial puncture	-	-	-	-	-

Intravenous therapy	-	-	-	-	-
Peripheral intravenous line	-	-	-	-	-
Central intravenous line	3.17 (2.36-4.27, <0.001)	-	-	-	-
Nasal oxygen therapy	-	-	-	-	-
Prior hospitalization	-	-	-	-	-
Rhinopharyngoscopy, laryngoscopy, esophagoscopy, hysteroscopy	-	3.60 (1.34-9.70)	-	-	-
Genitourinary and obstetric procedures	-	3.00 (1.81-4.98)	-	-	-
Any procedure	-	3.86 (3.31–4.50	1.98 (1.66–2.37)	-	-

Abbreviations: ENT = ear, nose and throat, GI = gastrointestinal, GU = genitourinary, OR = odds ratio, RD= risk difference.