1 AHA Science Advisory

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

1. **A Scientific Advisory from the American Heart Association**

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4. Bernard Prendergast, BM, BS, MD; Mark J. Dayer, MBBS, PhD; on behalf of the American
5. Heart Association Council on Lifelong Congenital Heart Disease and Heart Health in the
6. Young, Rheumatic Fever, Endocarditis and Kawasaki Disease Committee; Council on
7. Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing;
8. Council on Clinical Cardiology; and Council on Peripheral Vascular Disease
9. Abstract
10. There have been no published prospective clinical trials that have: 1) established an
11. association between invasive dental and non-dental invasive procedures (NDIPs) and risk of
12. infective endocarditis; or 2) defined the efficacy and safety of antibiotic prophylaxis
13. administered in the setting of invasive procedures in the prevention of IE in high-risk
14. patients. Moreover, previous observational studies that examined the association of NDIPs
15. with the risk of IE have been limited by inadequate sample size. They have typically focused
16. on a few potential at-risk surgical and non-surgical invasive procedures. However, recent
17. investigations from Sweden and England that used nationwide databases and demonstrated an
18. association between NDIPs, and the subsequent development of IE (particularly in high-risk
19. IE patients) prompted the development of the current Science Advisory.
20. **Key words:** AHA Science Advisory; endocarditis, non-dental invasive procedures, risk,
21. antibiotic prophylaxis
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# Introduction and Overview

1. Infective endocarditis is associated with a risk of devastating complications, and attempts at
2. its prevention in high-risk individuals are warranted. To date, prevention strategies have
3. focused on invasive dental procedures and resultant transient bloodstream infection due to
4. oral streptococci, and questioned whether antibiotic prophylaxis before dental procedures
5. could reduce the likelihood of IE. No prospective clinical trial has been conducted to
6. determine if there is an association between invasive procedures and the onset of IE and
7. whether antibiotic prophylaxis is effective in IE prevention. Key stakeholders, including the
8. American Heart Association (AHA) and the European Society of Cardiology (ESC), continue
9. to recommend antibiotic prophylaxis in high-risk individuals who undergo invasive dental
10. procedures. Recent extensive case-crossover analyses and cohort studies in large US
11. populations support this notion.1,2 However, there are no recommendations for a similar
12. approach for non-dental invasive procedures (NDIPs) due to a lack of supporting evidence.
13. Findings from two recently published nationwide investigations suggest that the link
14. between NDIPs and the risk of IE in high-risk patients (and the potential role of antibiotic
15. prophylaxis) should be revisited*.* Several NDIPs were strongly associated with the risk of IE
16. in a case-crossover study of >7,000 cases of IE derived from the Swedish National Patient
17. Register,3 and similar temporal associations were confirmed in >14,000 English patients with
18. IE.4 The present Science Advisory further addresses this question in light of the
19. 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.

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# 2 Current International Guidelines

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1. American Heart Association (AHA)/American College of Cardiology (ACC) (Table 1)
2. Despite a lack of clinical trial data supporting a link between invasive procedures and the risk
3. of development of IE, the AHA has endorsed the potential benefit of antibiotic prophylaxis in
4. 10 of the 11 iterations over the past 70 years. In the earliest (1955) document, antibiotic
5. prophylaxis was recommended for patients with rheumatic or congenital heart disease before
6. dental procedures and NDIPs, including removal of tonsils and adenoids, normal vaginal
7. delivery, and surgery on the gastrointestinal or urinary tract.5 The 1990 version6 was unique
8. in providing a more detailed description of specific NDIPs where antibiotic prophylaxis
9. should be considered in moderate- and high-IE-risk patients and was followed by similar
10. recommendations in 1997 using more simplified antibiotic regimens.7
11. A *major* shift in perspective came in 2007 (Table 1)8 in recognition of concerns
12. regarding antimicrobial stewardship, adverse reactions and increasing antibiotic resistance,
13. and the fact that antibiotic prophylaxis would likely prevent only a small number of IE cases.
14. The focus remained on patients at the highest risk of IE complications with weak
15. recommendations for the use of antibiotic prophylaxis before procedures involving
16. established infections of the genitourinary, gastrointestinal, skin, soft tissue, or
17. musculoskeletal tracts (Class IIb, Level of Evidence B), respiratory tract procedures
18. involving incision or biopsy in high-risk individuals (Class IIa, LOE C), and no use before
19. gastrointestinal and genitourinary procedures (Class III Level of Evidence B). Furthermore,
20. the most recent recommendations focused exclusively on preventing IE due to viridans group
21. streptococci with no mention of NDIPs.9

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1. European Society of Cardiology (ESC) Guidelines (Table 1)
2. Reflecting ACC/AHA guidance, ESC recommendations regarding the use of antibiotic
3. prophylaxis have become progressively more constrained. Thus, while the 2004 ESC
4. guidelines recommended AP for patients at moderate- and high-IE risk undergoing a broad
5. range of both dental and NDIPs,10 this position was revised in 2009 to match the AHA
6. guidelines restricting antibiotic prophylaxis to patients at high risk undergoing invasive
7. dental procedures11 – a position that was upheld in the latest ESC guideline recommendations
8. in 2015.12

9

1. UK Guidelines (Table 1)
2. The British Society for Antimicrobial Chemotherapy (BSAC) produced guidelines in 2006
3. that broadly paralleled 2004 ESC recommendations of antibiotic prophylaxis for a wide range
4. of procedures in high-IE-risk patients.13 The National Institute for Health and Care
5. Excellence (NICE), however, provided new guidance in 2008 that recommended the
6. *complete cessation* of antibiotic prophylaxis for all procedures in all patients. A review in
7. 2015 reaffirmed this guidance, but it was softened one year later (to: “antibiotic prophylaxis
8. against infective endocarditis is not *routinely* recommended for people undergoing dental
9. procedures”) following a change in the UK law on consent.14 However, NICE provided no
10. guidance as to which situations should be considered “non-routine” or which antibiotic
11. regimens should be used.

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

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

4

1. Lacassin *et al* (1995)15
2. In a case-control study “to estimate the relative risk of IE associated with various medical,
3. surgical and dental procedures”,15 Lacassin *et al.* prospectively identified IE cases defined by
4. von Reyn’s criteria,16 and supplementary echocardiographic and histological findings to
5. strengthen diagnostic accuracy. The study included 171 cases and 171 matched control
6. patients recruited from cardiology or medical wards, and all procedures involving cutaneous
7. and mucosal surfaces were recorded. In the adjusted analysis, having a procedure (OR 1.6,
8. [1.01-2.53]) and having a surgical procedure (OR 4.7, [1.02-22]) within three months before
9. the diagnosis of IE or study entry were both associated with the risk of IE. Of note, this study
10. was undertaken when AP was used routinely, and analysis was not stratified according to IE
11. risk.

16

1. Strom *et al* 200017
2. In this case-control study, patients with community-acquired IE were compared with
3. community controls matched according to age, sex, and neighborhood of residence; people
4. who inject drugs were excluded. Among 287 selected patients, 273 completed an interview
5. and were compared with 273 controls. After adjustment for socioeconomic factors, pre-
6. existing valve disease, severe renal disease, and diabetes mellitus, only barium enemas
7. were significantly associated with the development of IE (adjusted OR, 11.9 [1.34–106], p=0.026)
8. among a wide variety of NDIPs (including bronchoscopy, lung biopsy, barium enema, upper
9. and lower GI endoscopy [including esophageal dilatation], gynecological surgery, urinary
10. catheterization, cystoscopy, lithotripsy, urinary and prostate surgery, sterilization/vasectomy,
11. cardiac procedures, other surgery, intravenous and nasal-oxygen therapy). Of note, barium
12. enema was frequently done within an IE workup, and colonic cancer/polyps were associated
13. with IE development.

3

1. Ammar *et al* 201318
2. A case-control study included 175 adult patients with definite IE, according to modified Duke
3. Criteria, and 175 matched adult controls without IE. They looked for a relationship between
4. several procedures and the development of IE. These included upper respiratory tract
5. procedures, gynecological surgery (n=73 cases, n=72 controls), urinary catheterization, other
6. genitourinary procedures, cardiac catheterization, peripheral intravenous lines, central
7. intravenous lines, and “other procedures”. The only procedure associated with an increased
8. risk of IE was the presence of a peripheral venous catheter (OR 2.78 [1.32-5.02]).

12

1. Mohee *et al* 201419
2. This single-center case-control study was conducted to determine whether urological
3. procedures were associated with the development of IE and compared four distinct groups of
4. IE patients (n=384) classified according to the causative bacterial species (enterococci,
5. coagulase-negative staphylococci, *Streptococcus bovis*, oral streptococci) with control cases
6. caused by bacteria of unlikely urological origin. Confounding by factors predisposing to IE
7. was therefore minimal. Among a variety of procedures (including hemodialysis, upper and
8. lower GI procedures, and urological procedures), the multivariable analysis demonstrated that
9. patients undergoing urological procedures were significantly more likely to develop IE due to
10. enterococci (OR 8.56 [3.69-19.85], p<0.001).

23

1. Garcia-Albeniz *et al* 201620
2. Patients aged 70-79 years with no history of colorectal cancer, prior colectomy, or IE were
3. derived from a random sample (20%) of Medicare beneficiaries in this cohort study,
4. specifically addressing the risk of developing IE after colonoscopy. The authors compared
5. the 3-month IE risk between individuals who underwent colonoscopy for screening,
6. surveillance, or diagnostic purposes versus those who did not after standardizing for several
7. potential confounders, including comorbidities. They further classified individuals with a
8. history of valve disorders, structural heart disease, intra-vascular devices, or end-stage renal
9. disease as “high-risk”. Importantly, this definition is inconsistent with “guidelines” criteria
10. for high-IE risk and is more consistent with moderate-IE risk. There were 1,013 IE cases in
11. the symptomatic population (n=994,971), 179 in the surveillance population (n=721,881),
12. and 279 in the prevention population (n=1,462,360). The investigators concluded that the risk
13. of developing IE after colonoscopy was increased in individuals with IE risk factors and GI
14. symptoms but acknowledged that it remained unclear whether colonoscopy or the colonic
15. lesion was responsible for this association.

12

1. Sun *et al* 201721
2. All children born with congenital heart disease in Taiwan between 1997 and 2005 (diagnosed
3. before three years of age) were followed until 2010. IE diagnosis or death and invasive
4. cardiovascular procedures performed during the six months before this index date were
5. identified using the National Health Research Institutes of Taiwan database. Among 24,729
6. children with congenital heart disease, 273 were newly diagnosed with IE (overall incidence
7. 111.3 per 100,000 person-years), with the highest risk in those undergoing cardiovascular
8. procedures and central venous catheter insertion.

21

1. Janszky *et al* 20183
2. In this case-crossover study, patients aged > 20 years who received in-patient treatment for IE
3. between 1998 and 2011 were identified in the Swedish National Patient Register, and those
4. who had undergone procedures that might be confounded with IE (such as central venous or
5. arterial catheter insertion) were excluded. Case and control periods were defined as 0-84 days
6. and 365-449 days before admission. An inpatient or outpatient invasive procedure was more
7. likely in the 7013 patients with IE during the case period (12 weeks) before developing IE
8. than during the control period a year before. Therapeutic procedures involving the skin, blood
9. transfusion and various operations, and diagnostic procedures (bone marrow puncture,
10. coronary angiography, and some modes of endoscopy [especially bronchoscopy]) were
11. associated the highest risk of IE in the subsequent three months, and risk differences were
12. much greater in those at high IE-risk.

7

1. Thornhill *et al* 20224
2. National admissions data included 14,731 cases of IE identified between 2010 and 2016 in
3. England and all invasive procedures performed on these individuals in the 15 months before
4. admission. The incidence of invasive procedures during the three months immediately before
5. IE admission (case period) was compared with the incidence during the preceding 12 months
6. (control period) to determine whether the odds of developing IE were increased within three
7. months of an invasive procedure. Two analytic techniques – a “step” and a “hinge” model –
8. were employed, the latter correcting for a general increase in the number of procedures over
9. time. The odds of developing IE were significantly elevated after several procedures,
10. including cardiac implantable electronic device procedures, upper and lower GI endoscopy,
11. bone marrow biopsy, blood transfusion, and bronchoscopy. The study also demonstrated that
12. the increased IE risk attributable to these procedures was much greater in subjects at high-IE
13. risk (Figure 1).

21 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.

# 22 Current Position

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1. Eight studies that included a cohort (1), case-control (5) or case-crossover design(2)
2. evaluated non-dental procedures and the associated risk of IE and were reviewed in this
3. Science Advisory (Tables 2a&b).3,4,17-22 The results from two of them3,4 were key in
4. prompting a call for this Science Advisory and deserve further highlighting. Both utilized a
5. case-crossover design which enhanced the control of potential confounders and comorbidities
6. that were stable over time. In addition, both investigations included nationwide cohorts,
7. which eliminated concerns about adequate cohort size for statistical evaluation, and
8. mandatory registration of admissions and invasive procedures prevented bias due to self-
9. selection and biased recall which are important limitations in case-control studies. Both
10. evaluated an extensive list of healthcare-related procedures. Patients labelled as high-risk of
11. IE were at increased risk of developing IE after several non-dental invasive procedures,
12. including CIED implantation, gastrointestinal endoscopy, and bronchoscopy (Figure 1).
13. There are limitations to both the Janszky and Thornhill publications. The indications
14. for invasive procedures and the effect of these procedures were not able to be separated in
15. these studies which might have introduced spurious associations. However, investigators
16. made substantial efforts to exclude the likelihood of procedures being performed as part of
17. the diagnosis or management of IE in the analyses. For example, all procedures were
18. excluded if performed during an IE-related hospital admission and before an IE diagnosis.
19. Procedures associated with attempts to diagnose IE, for example, transesophageal
20. echocardiogram (TEE) (and some other procedures), were excluded whenever they occurred
21. (Including in the weeks/months before an IE-related admission to hospital). There was a
22. strong association between TEE performed in the three months before an IE admission and
23. the subsequent development of IE. This could arguably represent a true association with
24. subsequent IE development. In addition, procedures performed after an IE diagnosis was
25. made but were done for IE management were also excluded. Electronic health records were
26. not available for review, and diagnoses were based on ICD coding. Moreover, there was no
27. information about the use of antibiotics as prophylaxis or treatment to prevent IE.
28. These latter two limitations may have led to an underestimation of effects. A
29. lack of available microbiologic data in both investigations was also an important
30. shortcoming. This would help validate an association between procedure and development of
31. IE, based on the well-recognized distribution of organisms as unique colonizers of various
32. anatomical locations.
33. The remaining six studies (Tables 2a & b) deserve comment. In contrast to the
34. publications mentioned above that examined numerous NDIPs, one investigation20 focused
35. only on colonoscopy and the risk of IE. It included a large population of Medicare
36. beneficiaries; 1471 patients had IE. Based on their definition of patients with “high IE-risk”
37. (History of valve disorders, structural heart disorders, intravenous devices, or end-stage renal
38. disease), there was an increased risk of IE in the high IE-risk patients who underwent a
39. polypectomy or a biopsy during colonoscopy in the setting of recent gastrointestinal
40. symptoms.
41. Mohee and colleagues19 focused only on urological procedures that included 384
42. patients with IE. They demonstrated an association between a procedure and the development
43. of IE due to enterococcal species. Whether the procedure or the underlying urological
44. disorder was responsible for the IE episode was not determined.
45. The population-based case-control study by Strom and colleagues17 also suffered from
46. limitations. The number of cases and controls for evaluation of individual procedures was too
47. small to secure an appropriate analysis of their risk in predisposing to IE development. This
48. was also the problem with both the Lacassin and the Ammar studies.15,18

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# Future Considerations

1. The novel evidence assessed in this Science Advisory suggests that the role of NDIPs as risk
2. factors associated with the subsequent development of IE, particularly in those at high-IE
3. risk, should be re-evaluated. The new data indicate that certain invasive medical/surgical
4. procedures have the potential to cause IE, particularly in those at high-IE risk. These findings
5. have at least two potential implications in clinical practice. First, there is a need to educate
6. clinicians performing these procedures on the potential risk posed by them in high IE-risk
7. patients. This would include scrupulous attention to sterility and infection prevention and
8. control interventions normally undertaken with these procedures. For procedures that involve
9. repeated or long-term insertion of transcutaneous catheters, e.g., hemodialysis, insertion of
10. central venous catheters etc., scrupulous sterility and infection prevention and control
11. precautions are likely to be particularly important in reducing the risk that they pose to high
12. IE-risk patients; the repeated or long-term use of antibiotics to reduce the risk of IE
13. associated with these procedures is impractical and has been associated with the promotion of
14. antibiotic resistance among colonizing strains. For procedures where antibiotics are routinely
15. prescribed to prevent post-operative surgical site infections, e.g., insertion of CIEDs, ERCPs,
16. trans-urethral and trans-rectal prostate procedures, etc., compliance with post-operative
17. infection prevention and control guidelines, and consideration of antibiotic regimens that
18. might also help to prevent IE, may be particularly important in individuals at high IE-risk.
19. Indeed, there may be reason to consider using augmented or supplemental methods to prevent
20. surgical site infections in this group of patients, e.g., using an antibiotic-impregnated
21. envelope to prevent CIED infections.23
22. For NDIPs, where there may be a significantly increased risk of IE in those at high
23. IE-risk, but currently there are no specific post-operative infection prevention guidelines, e.g.,
24. most endoscopy procedures, it may be appropriate to consider if there are specific actions that
25. could be taken to reduce the IE-risk in high-risk patients. Guidelines committees may wish to
26. consider if individuals at high IE risk undergoing NDIPs would benefit from AP regimens
27. targeted against typical colonizing bacteria.
28. Second, there is a need to educate and alert primary and secondary care physicians to
29. the possibility of IE occurring in high IE-risk individuals in whom NDIPs have recently been
30. performed (particularly in the preceding three months). This alertness is important to ensure
31. the earliest possible diagnosis and treatment of IE in high-risk individuals to obtain optimal
32. treatment outcomes.
    1. Because randomized clinical trials have not been feasible, largely due to the low
    2. incidence of IE, high-quality large observational studies are essential to help validate further
    3. advice and guidance, particularly related to high-risk procedures and high IE-risk patients.
    4. In summary, we propose that there is sufficient evidence associating certain NDIPs
    5. with the subsequent occurrence of IE, particularly in those at high IE risk, to warrant a re-
    6. evaluation of IE prevention advice.
    7. **Acknowledgments** The writing group thanks Danielle J. Gerberi, MLS, AHIP, for her expert assistance in performing the literature search.

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

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Guidelines/Recommendations** | **AHA 199014** | **AHA 19977** | **AHA 20078** | **AHA 20219** | **ESC 199524** | **ESC 200410** | **ESC 200911/1512** | **UK – BSAC 200613** | **UK – NICE 2008/2015/201611** |
| **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** | **Lacassin15** | **Strom17** | **Ammar18** | **Mohee19** | **Garcia-Albeniz20** |
| **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

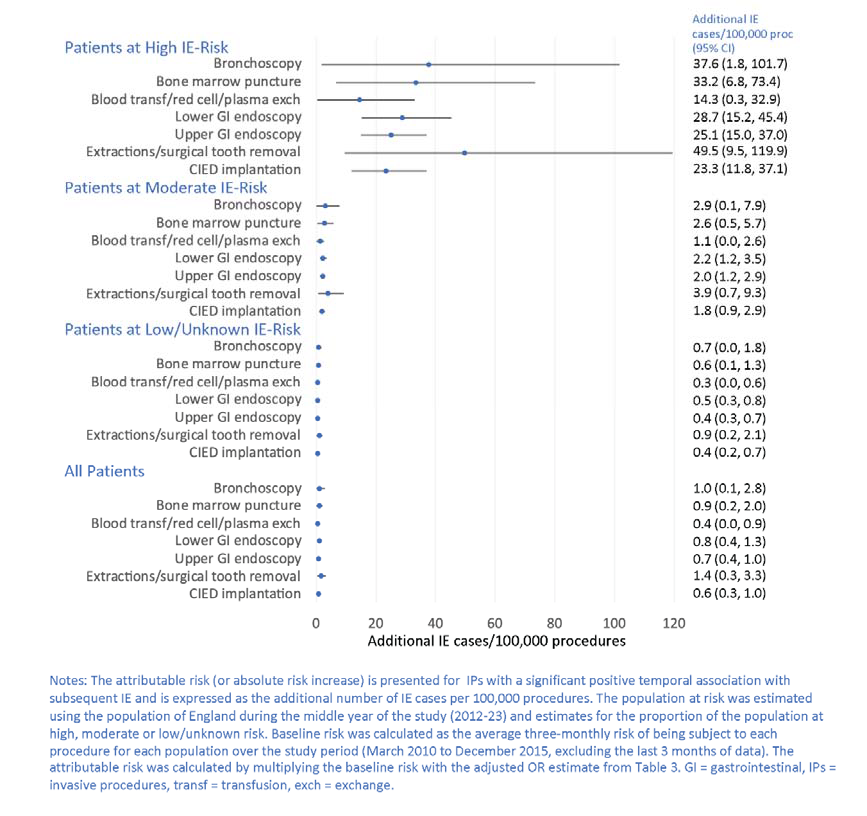
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Sun21** | **Janszky3** | **Janszky3** | **Thornhill4** | **Thornhill4** |
| **Year** | **2017** | **2018** | **2018** | **2022** | **2022** |
| **Subgroup** | N/A | Inpatient IPs | Outpatient IPs | Step model | Hinge model |
| **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.

Figure 1. Predicted additional IE cases per 100,000 procedures according to IE-risk



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