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Endocarditis prophylaxis – indications, application and current controversies

Short title: **Endocarditis prevention**

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Abstract

Links between infective endocarditis (IE) and dental and other invasive procedures were first identified in the 1920s, leading to the first recommendation by the American Heart Association (AHA) in 1955 that antibiotic prophylaxis (AP) should be used to prevent IE. Recognising the weak evidence to support this practice and the wider risks of anaphylaxis and antibiotic resistance, guidelines in the USA and Europe have been rationalised in the last two decades, restricting the use of AP to the highest risk patients (and the complete cessation of AP for all invasive procedures in the UK). However, recent data demonstrate that AP is safe and effective in reducing the incidence of IE in high-risk individuals undergoing invasive dental procedures and support current European Society of Cardiology (ESC) and AHA guidance,. Nonetheless, debate continues, and several questions remain. Which patients should receive AP? Which dental and non-dental procedures require AP? And which AP regimens and other preventive measures are safest and most cost-effective? In this narrative review, we address these controversies with reference to recent literature and clinical experience.

Keywords:

Infective endocarditis, antibiotic prophylaxis, dental procedures, guidelines, prevention, risk

Abbreviations:

ADA = American Dental Association

ADR = Adverse drug reaction

AHA = American Heart Association

AP = Antibiotic prophylaxis

BSAC = British Society for Antimicrobial Chemotherapy

ESC = European Society of Cardiology

HACEK = Species of *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*

HIPAA = Health Insurance Portability and Accountability Act

ICD = International Classification of Disease

IDPs = Invasive dental procedures

IDU = Injection drug use

IE = Infective endocarditis

NDIPs = non-dental invasive procedures

NHS = National Health Service (UK)

NICE = National Institute for Health and Care Excellence (UK)

OVGS = Oral viridans group streptococci

RCT = Randomised controlled trial

UK = United Kingdom

US = United States of America

Introduction

Infective endocarditis (IE) is an infection of the endocardium characterised by the development of infected heart valve vegetations with an annual incidence of 3-10 per 100,000 and poor prognosis (in-hospital mortality 15-20%, rising to approximately 30% at one year).¹⁻³ Prolonged high-dose intravenous antibiotics have been the mainstay of treatment, and valve repair or replacement is required in 24-50% of cases.¹⁻⁴ Morbidity is high in those who survive, with a significant risk of re-infection or relapse as well as progressive deterioration in valve function leading to heart failure and the need for further medical or surgical intervention.¹⁻³ In this context, prevention strategies have always been a priority, including the use of antibiotic prophylaxis (AP) prior to invasive medical and dental procedures producing bacteraemia that might lead to IE. However, evidence concerning the efficacy of AP has been difficult to obtain due to the rarity of the condition and challenges preventing randomised controlled trials (RCT). Expert opinion, lack of evidence and controversy have therefore plagued IE prevention guidelines since their inception. We examine these issues in this narrative review.

Background

In 1923, Lewis and Grant first suggested that invasive dental procedures (IDPs) could cause IE by releasing oral viridans group streptococci (OVGS) into the circulation.⁵ This proposal was confirmed in 1935 when Okell and Elliott demonstrated that 61% of patients had positive blood cultures following dental extractions and isolated OVGS from the vegetations of 40-45% of IE patients.⁶

In 1943, Northrop and Crowley suggested that sulfathiazole could reduce the risk of IE following IDPs in patients with rheumatic heart disease.⁷ Soon after, the efficacy of penicillin in reducing OVGS bacteraemia following IDPs was demonstrated,^{8,9} paving the way for the first American Heart Association (AHA) AP guidelines in 1955.¹⁰

Early guidelines on the use of antibiotic prophylaxis (AP) to prevent IE

The first AHA guidelines identified high-risk patients (those with rheumatic or congenital heart disease) and high-risk procedures (“dental extraction and other dental manipulations which disturb the gums, the removal of tonsils and adenoids, the delivery of pregnant women, and operations on the gastrointestinal or urinary tracts”) and recommended intramuscular penicillin 30 minutes before the procedure or a complex oral penicillin regimen starting 24 hours before the procedure and continuing for 5 days.¹⁰ Over the next two decades, four more iterations of the AHA guidelines appeared,¹¹⁻¹⁴ and the recommendation that AP should be given for childbirth was deleted.

The move from parenteral to oral antibiotic prophylaxis

The first UK AP guidelines were produced by the British Society for Antimicrobial Chemotherapy (BSAC) in 1982¹⁵ and marked a shift from the complex parenteral or multi-dose oral AP regimens recommended by the AHA guidelines.¹⁶ Instead, a single 3g oral dose of amoxicillin was recommended one-hour before the procedure, whilst parenteral regimens were reserved for those undergoing general anaesthesia. Subsequent AHA and European Society for Cardiology (ESC) guidelines adopted the simpler oral regime.

Defining risk status in patients with different pre-disposing cardiac conditions

An expert group published the first European consensus IE guidelines in 1995.¹⁷ Addressing the role of AP, the guidelines classified patients at high- (those with prosthetic valves, previous IE or cyanotic congenital heart disease) or moderate/intermediate-risk (those with valvular heart disease, including mitral valve prolapse with regurgitation and bicuspid aortic valve) of IE. They also stressed the importance of giving AP before dental procedures associated with gingival bleeding, tonsillectomy, adenoidectomy, and some gastrointestinal and urological procedures.

The 1997 AHA guidelines were in close overall consensus with European guidance, endorsing the stratification of patients into high-, moderate- and negligible-risk categories,¹⁸ and adding patients with surgically constructed systemic pulmonary shunts and conduits to the high-risk category. For the first time, the AHA guidelines recommended a single 2g oral dose of amoxicillin as the preferred AP regimen for all patients at moderate- or high-risk of IE undergoing dental, oral, respiratory or oesophageal procedures (with a single 600mg oral dose of clindamycin for those allergic to penicillin). The 2004 ESC guidelines matched these recommendations and most international guidelines became closely aligned.¹⁹

Restricting the number of individuals receiving AP

New UK AP recommendations provided by BSAC in 2006²⁰ argued that there was no randomised controlled trial (RCT) evidence supporting the use of AP, and recommended that its use before invasive dental procedures should be restricted to patients at high IE-risk. However, they continued to recommend AP for those at moderate or high IE-risk undergoing invasive gastrointestinal, genitourinary, gynaecological and respiratory procedures.

The suggestion that AP cover should be restricted caused outrage amongst UK cardiologists,²¹ and the 2006 BSAC guidance was referred for review by the newly formed National Institute

for Health and Care Excellence (NICE). NICE revealed the outcome of its review in March 2008 and recommended complete cessation of AP for all patients and all procedures.²³ It gave as the reasons, (i) the lack of evidence for AP efficacy, (ii) concern that the risk of adverse reactions (ADR) might outweigh any benefit of AP, and (iii) their health economic assessment that concluded AP was not cost-effective.²⁴ This recommendation simplified patient management for UK dentists and was rapidly adopted.^{25, 26}

While the NICE review was underway, the outcome of the 2007 AHA guideline review was announced.²⁷ Like BSAC, the AHA recommended restriction of AP to patients at highest risk of IE or its complications, and cessation for those at moderate-risk (those with a history of rheumatic fever, native valve disease e.g. mitral prolapse, congenital valve anomalies e.g. bicuspid aortic valve, or hypertrophic cardiomyopathy) and for many non-dental invasive procedures (including all genitourinary and gastro-intestinal procedures). Closely mirroring these recommendations, the 2009 ESC guidelines also restricted AP to those at highest IE-risk.²⁸ In both cases, the reasons for restriction of AP use were, (a) the lack of evidence of AP efficacy – particularly in those at moderate-risk, (b) concerns about the risk of ADR to AP antibiotics, and (c) broader concerns that unnecessary AP use could promote antibiotic resistance. However, these considerations were balanced by the clinical priority to prevent IE in those at highest risk. Nevertheless, the 2007 AHA and 2009 ESC guidelines were widely emulated and adopted globally. With the notable exception of Sweden, where NICE recommendations against AP were adopted in 2012, but abandoned four years later when evidence emerged of increasing IE-incidence in England.²⁹

In Japan, there was concern about the ongoing risk of IE in moderate-risk individuals and national guidelines continued to recommend AP in both high- and moderate-risk patients.³⁰

Similarly, Australian IE prevention guidelines continued to recommend AP cover for dental and other invasive procedures in individuals at high IE-risk, but included patients with rheumatic heart disease given its high prevalence in young and middle-aged Aboriginal and Torres Strait Island peoples with a high burden of concomitant medical comorbidities and difficulties accessing medical and dental care.³¹

The impact of changing AP guidelines

The best evidence for the efficacy of AP would come from a randomised placebo-controlled trial (RCT), but for cost and logistic reasons such a trial has never been performed and is unlikely in the foreseeable future. Hundreds of thousands of high-risk individuals would need to be randomised to placebo or AP to detect a statistically significant effect³² and there are serious ethical concerns about randomising high-risk individuals to placebo in countries where AP is the standard of care.³²

Nevertheless, many observational studies have attempted to determine whether changes in AP guidelines have altered IE-incidence, using a variety of methodologies with specific advantages and limitations (please refer to the Supplementary Appendix S1 for an explanation of these methodologies). Whilst some of these studies have identified an increase in IE-incidence that may be partly attributed to reduced use of AP, there are multiple alternative explanations, including improved diagnosis, increasing numbers of individuals at high-risk of IE due to interventional cardiac procedures or intravenous drug use, and an aging population with more comorbidities and risk factors for IE.³³⁻³⁵

Most time course studies have been limited by one or more of the following factors: small sample size, short follow-up period, failure to account for AP prescribing (which could hide any

effect on IE-incidence) or the dilution of high-risk populations (where any effect would be focussed) in the much larger low/no-risk general population (where any effect would not be expected), and inability to specifically identify cases caused by OVGS. Indeed, even adequately powered studies are often unable to distinguish between the different potential causal factors. As with all observational studies, causal relationships cannot be proven, and even when attempts have been made to address possible confounders, the existence of residual confounders cannot be excluded.

In the UK, an observational study published 7 years after NICE had recommended against the use of AP demonstrated an 88% fall in AP prescribing and a significant increase in IE-incidence ($p < 0.0001$) over and above the pre-existing upward trend.²⁹ The same study suggested an extra 419 IE-cases per year in England than would have been expected if AP prescribing had remained unchanged ($p < 0.0001$; 95% CI 117-743). Moreover, this increase was greatest (and most significant) in those at high IE-risk ($p < 0.001$). Although these data did not prove that the increase was caused by the fall in AP prescribing, it did raise legitimate concerns about the guidance and prompted both NICE and the ESC to review their guidance.

Having evaluated the same evidence, these organisations announced their updated recommendations almost simultaneously in September 2015. NICE determined there was insufficient new evidence to change their guidance and continued to recommend against AP.³⁶ In contrast, the ESC concluded that “the weight of evidence and opinion is in favour of the efficacy and usefulness of AP in preventing IE in those at high-risk... and AP should be given before invasive dental procedures to all patients at high-risk of IE”.³⁷ The ESC considered but rejected the 2008 NICE guidance because of (a) remaining uncertainties regarding estimations of IE-risk, (b) the worse prognosis of IE in high-risk patients, and (c) the fact that high-risk

patients account for a very small proportion of those previously covered by AP (thereby reducing the number exposed to any possible harmful adverse effects).

How could the ESC and NICE differ so widely in their interpretation of the same evidence?

The ESC and AHA guideline committees included cardiologists, infectious disease specialists, cardiothoracic surgeons, dentists and other health professionals. Both committees review all the available evidence (including animal and observational studies) before reaching their conclusions. In both cases, the relevant professional bodies review the guidance intensely before submission to international peer reviewed journals where they are subjected to further review.

The primary purpose of NICE is to evaluate the cost-effectiveness of drugs and technologies for use in the UK National Health Service. Their AP review was undertaken by a standing committee that deals with a variety of guidelines but without specific expertise in IE. Moreover, NICE protocols required RCT data in 2015 and excluded animal studies and even the best observational studies on account of their 'low quality'.³⁸ Without new RCT data, NICE protocols prevented any change in guidance.

Following this decision, NICE came under pressure from patients, politicians, cardiologists and dentists to reconsider and changed the wording of the guidance in July 2016 to "AP against IE is not recommended routinely for people undergoing dental procedures".³⁹

The word 'routinely' was ambiguous and caused confusion for dentists, cardiologists and patients – furthermore, NICE provided no information as to what constituted "routine" or "non-routine" care. To fill this vacuum, the Scottish Dental Clinical Effectiveness Programme (SDCEP)

produced advice for dentists on how to implement the NICE guidelines in 2018.⁴⁰ This advice asserted that “The vast majority of patients at increased risk of IE will not be prescribed antibiotic prophylaxis. However, for a very small number of patients, it may be prudent to consider antibiotic prophylaxis (non-routine management) in consultation with the patient and their cardiologist or cardiac surgeon” and was later approved by NICE and adopted by the Chief Dental Officers for England, Scotland, Wales and Northern Ireland. The patients that SDCEP suggested should be considered for AP were the same as those recommended by the ESC and AHA, but dentists were told to consider AP only if advised to do so by the patient’s cardiologist or cardiac surgeon and, even then, to “discuss the potential benefits and risks of prophylaxis for invasive dental procedures with the patient to allow them to make an informed decision about whether prophylaxis is right for them.” However, neither NICE nor SDCEP provided any information about the risks and benefits of AP that clinicians could use to inform their patients, leaving patients without the facts they needed to make important treatment choices.

[New evidence](#)

[Association between invasive dental procedures \(IDPs\) and IE](#)

Given the difficulties in performing RCTs or drawing conclusions from time-course studies examining the effect of guideline changes, several recent studies have attempted to investigate whether there is an association between IDPs and the development of IE (given that such an association is essential if AP is to have any benefit). Unfortunately, most of these were underpowered to detect such an association or performed in countries where AP is still recommended (potentially obscuring any association). Nonetheless, some very large population studies have identified an association, even in countries where AP is still

recommended. See Supplementary Appendix S1 for an explanation of the different study methodologies, their advantages and limitations.

A 2017 French study compared IDP incidence in the 3 months preceding 73 OVGS-IE cases and 192 controls with IE caused by other bacteria.⁴¹ Cases were significantly more likely to have undergone IDPs in the 3 months before developing IE (OR 3.3, 95% CI 1.2-9.3). A second cohort and case-crossover study focused on 138,876 patients with prosthetic valves, demonstrating no significant increase in OVGS-IE in the 3-months following IDPs.⁴² However, there was a significant association between IDPs and subsequent IE in the case-crossover study of 648 prosthetic valve patients who developed OVGS-IE (OR 1.7, 95% CI 1.1-2.6, $p=0.03$), despite AP use before only half of IDPs. The authors concluded that both studies suggested that “invasive dental procedures may be associated with oral streptococcal infective endocarditis although the magnitude of this association remains uncertain”.

A subsequent Korean study of patients with implanted cardiac electronic devices found that IDPs were associated with a significantly increased risk of IE (OR 1.75, 95% CI 1.48-2.05; $p<0.001$) in a population where only 1.24% of IDPs were covered by AP.⁴³ A self-controlled case study in Taiwan also identified a significant association between IDPs and IE (age-adjusted incidence rate-ratio 1.14, 95% CI 1.02-1.26) but did not report the extent of AP use.⁴⁴

Since AP has not been recommended in the UK since 2008, any association between IDPs and IE should be fully exposed. A nationwide case-crossover study of dental extractions performed in hospital out-patient clinics found a significant association with the development of IE (OR 2.1, 95% CI 1.2-3.8, $p<0.05$),⁴⁵ and calculated the additional number of IE-cases likely to occur following IDPs in those at low (0.9/100,000 procedures, 95% CI 0.2-2.1), moderate

(3.9/100,000 procedures, 95% CI 0.7-9.3) and high IE-risk (49.5/100,000 procedures, 95% CI 9.5-119.9).⁴⁵

A nested case-crossover and case-control study performed in Sweden (where AP was not recommended between October 2012 and March 2016) was unable to confirm an association between OVGS-IE and IDPs in those at high-risk.⁴⁶ However, the sample size was small with only 240 cases in the case-control group (of whom only 6 underwent extractions and 5 scaling procedures). Similarly, there were only 4 extractions and 4 scaling procedures in the 3-month case period, and 7 extractions and 9 scaling procedures in the 6-month control period among 213 participants in the case-crossover study. The authors acknowledged that “a study with larger sample size could clarify whether there is a lack of association”. To achieve this sample size, patients were drawn from a 51-month period when AP was recommended for all Swedish patients at risk of IE undergoing IDPs (July 2008- October 2012) and a 22-month period when AP was recommended if advised by the patient’s cardiologist (March 2016- January 2018), as well as a 42-month period when AP was not recommended. Importantly, even when not recommended, AP was still prescribed for 59% of IDPs in high-risk patients. It is likely, therefore, that the study was underpowered and that use of AP obscured any association between IDP and IE.

A large study of US patients with employer-provided medical and dental insurance cover used case-crossover and cohort methodologies.⁴⁷ Case-crossover analysis of 3,774 patients with IE found a significant association between IDPs and the development of IE in high-risk individuals over the succeeding 30 days (OR 2.0, 95% CI 1.6-2.5, $p=0.002$). This association was strongest following dental extractions (OR 11.1, 95% CI 7.3-16.7, $p<0.0001$) and oral surgical procedures (OR 50.8, 95% CI 20.8-124.0, $p<0.0001$). Furthermore, the 8 million patient cohort study found

that the likelihood of developing IE was significantly higher in the 30 days following extractions (OR 9.2, 95% CI 5.5-15.9, $p<0.0001$) and oral surgical procedures (OR 20.2, 95% CI 11.2-36.7) in high-risk patients (who only received AP for 32.6% of IDPs).⁴⁷

In a similar study of US Medicaid patients,⁴⁸ case-crossover analysis of 2,647 IE-cases identified an association between IDPs and the development of IE within 30 days in those at high-risk. Again, this association was particularly strong following extractions (OR 3.7, 95% CI 2.7-5.3, $p<0.005$) and oral surgical procedures (OR 10.7, 95% CI 5.2-21.9, $p<0.0001$). The incidence of IE was also increased in the 30 days following IDPs in those at high IE-risk in the cohort study of 1.68 million individuals, particularly following extractions (OR 14.2, 95% CI 5.4-52.1, $p<0.0001$) and oral surgical procedures (OR 30.0, 95% CI 9.6-119.3).⁴⁸ Furthermore, only 25.9% of IDPs in high-risk patients were covered by AP.

A recent German registry found that individuals who underwent IDPs in the 3-months before the diagnosis of IE were significantly more likely to develop OVGS IE than controls ($p=0.001$), while controls were significantly more likely to develop staphylococcal or enterococcal IE.⁴⁹

Taken together, these studies support an association between IDPs and the subsequent development of IE, particularly in high-risk patients. More specifically, the data show that the risk of developing IE after IDPs is 4 and 50 times greater in those at moderate and high-risk, respectively, than in the general low-risk population.

Efficacy of Antibiotic Prophylaxis

The two large US studies were able to determine whether or not AP cover was prescribed for each dental procedure and thereby quantify the effect of AP on IE-incidence. In high-risk patients with employer-provided medical/dental cover, AP significantly reduced IE-incidence

following IDPs (OR 0.4, 95% CI 0.2-0.6, $p=0.002$), particularly extractions (OR 0.1, 95% CI 0.0-0.3, $p<0.0001$) and oral surgical procedures (OR 0.1, 95% CI 0.0-0.4, $p=0.002$; Figure 1a).⁴⁷ Furthermore, AP also significantly reduced IE-incidence following IDPs in high IE-risk Medicaid patients (OR 0.2, 95% CI 0.1-0.5, $p<0.0001$), particularly extractions (OR 0.3, 95% CI 0.1-0.8, $p<0.01$; Figure 1b).⁴⁸ The number needed to prevent (NNP), i.e. the number of IDPs, extractions or oral surgical procedures requiring AP cover to prevent one case of IE was 1536, 125 and 45, respectively, for those with employer-provided medical/dental cover, and 244, 143 and 71 for Medicaid patients (Figure 1).⁴⁸

Two recent systematic reviews also examined the efficacy of AP, one determining that AP was effective in reducing IE-risk following IDPs (observing that no high-risk patients developed IE in studies where all such patients received AP),⁵⁰ and the other (a meta-analysis) that AP was associated with significantly lower risk of IE after IDPs in high-risk individuals (pooled RR, 0.41; 95% CI, 0.29-0.57; p for heterogeneity =0.51; I^2 , 0%).³³

In sum, these recent studies, systematic reviews and meta-analyses provide the best evidence to date that AP significantly reduces the likelihood of IE following IDPs in high-risk individuals.

Risk of adverse drug reactions

The original NICE estimate of 20 fatal ADRs/million AP prescriptions and 20,000 non-fatal ADRs/million prescriptions²³ relied on out-dated estimates of ADR associated with penicillin (all penicillin types, doses, durations, indications and routes of administration).⁵¹⁻⁵³ These estimates led them to conclude that “antibiotic prophylaxis against IE for dental procedures may lead to a greater number of deaths through fatal anaphylaxis than a strategy of no antibiotic prophylaxis, and is not cost-effective.”

Soon after the 2015 NICE guideline review, however, new UK data quantified the ADR risk following the single 3g oral dose of amoxicillin used for AP and showed a substantially lower incidence of ADR.⁵⁴ No fatal ADRs were reported after 3 million amoxicillin AP prescriptions with only 22·6 non-fatal ADRs/million prescriptions. These findings were confirmed in other French and UK national studies that reported no deaths following amoxicillin AP.^{55, 56}

Antimicrobial resistance (AMR)

AMR is a major concern that may deprive us of effective antibiotics to treat and prevent infections.⁵⁷ Antibiotic stewardship programmes limit antibiotic prescribing to appropriate situations by ensuring use of the right antibiotic (appropriate spectrum of activity to treat the infection) at the right dose (sufficient to eradicate the organism while minimising side effects) for the shortest duration (compatible with effective treatment).

AMR is a particular problem with *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Streptococcus pneumoniae* infections,⁵⁸ but fortunately it is much less common with OVGS.⁵⁸ However, inappropriate use of amoxicillin to treat dentoalveolar infections merits attention as a potential source of AMR. Amoxicillin is the most widely prescribed dental antibiotic and prescriptions to treat dental infections substantially exceed its use for AP in most countries (despite guidelines recommending these infections should be treated surgically by means of extraction, endodontic treatment or incision and drainage).⁵⁹⁻⁶¹ Most guidelines recommend narrower-spectrum penicillins (such as phenoxymethylpenicillin) rather than amoxicillin (which is often used at too low a dose for too long, further increasing the likelihood of AMR).⁵⁹⁻⁶¹ Inappropriate use of amoxicillin to treat dental infections may also increase the selection of amoxicillin-resistant oral streptococci (although this effect is temporary and usually resolves after 28-35 days).⁶²

Use of high-dose, short-duration amoxicillin regimes for AP (single 2g oral dose in most countries; 3g in the UK) carries a much lower risk of AMR than more prolonged courses of amoxicillin to treat dentoalveolar infections. Nonetheless, amoxicillin AP may temporarily increase the proportion of amoxicillin-resistant OVGS in saliva for up to 5 days,⁶³ although this appears to be less likely with a 3g dose.^{15, 64-66} Indeed, the 3g oral dose of amoxicillin is still recommended in the UK on account of the reduced potential for AMR, increased effectiveness against OVGS, and minimal ADR.^{15, 20, 40, 64-66} Unfortunately, the sugar-free 3g sachet of amoxicillin powder (mixed with water to make a flavoured drink with high patient acceptability) is unavailable in other countries. Further review of the most effective amoxicillin dose and formulation for AP is warranted to minimise AMR risk and ensure maximum effectiveness. Meanwhile, restriction of AP to those at high-risk in the wake of shifting guideline recommendations has reduced the number of eligible individuals by ~90%,^{29, 67} substantially reducing the number of unnecessary AP prescriptions while retaining its use in the smaller number of high-risk patients who derive most benefit.

[Recent Changes in Guideline Recommendations](#)

In 2021, the AHA published new guidelines, that were aimed mainly at dentists and focused on the prevention of OVGS IE,⁶⁸ recommending that AP was only used in high-risk patients undergoing IDPs (Tables 1 & 2). They also recommended that oral cephalexin (2g), azithromycin (500mg), clarithromycin (500mg) or doxycycline (100mg) should be used as an alternative to amoxicillin in patients with penicillin allergy,⁶⁸ rather than clindamycin which has a higher risk of ADRs, particularly *Clostridioides difficile* infection (Table 3).^{54, 68}

In 2023, the ESC guidelines recommended that high-risk patients should continue to receive AP before IDPs to reduce the risk of IE (Tables 1, 2).⁶⁹ Moreover, they upgraded the strength of

this recommendation from Class IIa (weight of evidence/opinion is in favour of usefulness/efficacy), i.e. “AP should be considered” to Class I (evidence and/or agreement that a given treatment or procedure is beneficial, useful, effective) i.e. “AP is recommended”. Based upon the evidence that had accumulated since 2015. Beyond these changes, they added a new Class IIa recommendation, “AP should be considered in patients who have undergone transcatheter mitral and tricuspid valve repair”, a new Class IIb recommendation “AP may be considered in heart transplant recipients”, and confirmed the AHA recommendation concerning alternatives to clindamycin for penicillin-allergic patients.⁶⁹

These changes resulted in consistent guideline recommendations around the world concerning the need for high-risk individuals to receive AP before IDPs (Tables 1, 2). Under pressure to reconsider its recommendations, NICE determined in late 2024 that full review of the evidence was unwarranted, but substantially changed the wording of their recommendation:

“AP against IE is not recommended routinely for people undergoing dental procedures

- For advice on AP for people at high-risk of IE undergoing dental procedures and for relevant patient information, see the implementation advice provided by the Scottish Dental Clinical Effectiveness Programme (SDCEP, part of NHS Education for Scotland). This advice was developed in conjunction with, and is endorsed by, NICE. It has been endorsed for use across the UK by the Chief Dental Officers of the UK.”

Current SDCEP advice is based on 2015 ESC guidance and is now being updated to account for the 2023 ESC update, with new recommendations anticipated in early 2026. The re-worded NICE guidance acknowledges (for the first time) that some patients are at high-risk of IE following IDPs and would benefit from AP. Moreover, NICE’s endorsement of SDCEP advice

means that the UK now concurs with most other countries in recommending AP before IDPs in patients at high-risk of IE.

Ongoing Controversies

High-risk individuals

A growing body of cohort, case-control, case-crossover and animal model data has established a link between IDPs and IE in high-risk individuals, and demonstrated the efficacy of AP in this setting. Given that adequately powered RCTs are not always possible for conditions such as IE, there is now a high degree of guideline consensus worldwide concerning the need for high-risk individuals to use AP before IDPs to reduce the likelihood of IE (see Tables 1-3).^{70, 71}

Moderate-/Intermediate-risk patients

Recent epidemiological data suggest that some predisposing cardiac conditions currently stratified as moderate- or intermediate-risk (Table 4) have a risk of IE that approaches that of classical high-risk conditions.⁷²⁻⁷⁵ European and US studies have also demonstrated an increase in IE-incidence in moderate-risk individuals following guideline changes recommending against the use of AP.^{67, 72} Indeed, recent Swiss data demonstrated that the proportion of OVGS IE-cases increased significantly in moderate-risk individuals following the recommendation to stop AP in 2008.⁷² The increase in OVGS IE-incidence was greatest in patients with congenital valve anomalies, consistent with Spanish data showing that patients with a bicuspid aortic valve or mitral valve prolapse are at significantly higher risk of OVGS IE.⁷⁵ These studies have led to suggestions that certain moderate-risk patients should receive AP (or be re-classified as high-risk)^{72, 75} as currently recommended in Japan³⁰ and for patients with rheumatic heart disease in Australia.³¹ Further studies are required to determine which moderate-risk patients benefit from AP and whether this approach would be cost-effective. The 2023 ESC guidelines reflect

these concerns and state that AP may be considered for such patients on an individual basis.⁶⁹ AP may also be considered in moderate-risk patients with other factors that increase their risk of IE, e.g. those with more than one moderate-risk condition, significant comorbidities (such as diabetes or immunosuppression) or other IE-risk factors (such as poor oral hygiene or haemodialysis).^{76, 77} Even when AP is not indicated, there is consensus that general prevention measures (Table 5) should be adopted in both high- and moderate-risk patients.⁶⁹

Invasive dental procedures versus daily activities

The risk posed by IDPs has largely been derived from microbiological studies that quantified the frequency of bacteraemia following different procedures. Whilst many such studies have been used to identify those IDPs most likely to pose a threat,⁷⁸ bacteraemia is a surrogate for IE-risk and tells us nothing about risk variation after different IDPs in different patient cohorts. Quantification of this risk requires large scale epidemiological studies, which are now underway.^{47, 48, 79}

One such recent study quantified IE-incidence following IDPs in nearly 10 million US citizens stratified according to IE-risk.⁷⁹ The incidence of IE in high-risk individuals in the first 4 months after an IDP was 2,195 IE cases/million procedures - approximately 125 times higher than in those at low IE-risk (OR 126.3, 95% CI 113.5-140.6, $p < 0.0001$). This risk was even greater following extractions (incidence 8,680 IE cases/million extractions, OR 171.4, 95% CI 136.7-214.8, $p < 0.0001$) or oral surgical procedures (incidence 13,458 IE cases/million procedures, OR 245.5, 95% CI 165.1-365.1, $p < 0.0001$), but significantly lower in moderate-risk individuals (and negligible in those at low-risk).

The IE-risk following other IDPs was also high, but significantly lower than after oral surgical procedures ($p < 0.0007$) or extractions ($p < 0.0067$). Even though there were slight differences in

IE-incidence following these procedures (periodontal probing, dental prophylaxis [supragingival scale and polish], sub-gingival scaling/root planing, endodontic or restorative dental procedures), none were statistically significant. Nevertheless, the odds of developing IE following any of them were 55-112 times greater than when the same procedure was performed in low-risk individuals. These quantitative data are particularly important for patients at the time of informed consent prior to IDPs.^{77, 80}

Since the mid-2000's, ESC and AHA guidelines have recommended that high-risk individuals receive AP before *"All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth, or perforation of the oral mucosa"*. Although most consider that this includes all professional dental cleaning procedures (including scaling and polishing), some commentators have questioned whether periodontal probing (basic periodontal examination), dental prophylaxis (cleaning) or supra-gingival scaling are as invasive as sub-gingival scaling and root planing.⁴⁰ However, both population data⁷⁹ and bacteraemia studies⁷⁸ show that the risk of developing IE following all of these procedures is equivalent. The most recent ESC guidelines provide appropriate clarification: *"At-risk dental procedures include dental extractions, oral surgery procedures (including periodontal surgery, implant surgery, and oral biopsies), and dental procedures involving manipulation of the gingival or periapical region of the teeth (including scaling and root canal procedures)"*.⁶⁹

Debate regarding the relevance of bacteraemia caused by daily activities, such as toothbrushing, flossing and chewing (particularly in those with poor oral hygiene), is longstanding. In 1935, Okell and Elliott noted the potential for both IDPs (extractions) and poor oral hygiene (particularly dental sepsis) to cause IE,⁶ but opinion has shifted over time. The advent of antibiotics led to a focus on the use of AP to prevent IE following IDPs, but opinion

moved in the opposite direction in the early 2000's, leading NICE to conclude that *“regular toothbrushing almost certainly presents a greater risk of IE than a single dental procedure because of repetitive exposure to bacteraemia with oral flora.”*²³

Although several studies have confirmed significant bacteraemia following daily activities, the incidence and scale of the bacterial load are less than following IDPs.^{78, 81, 82} Nonetheless, there is clear evidence that poor oral hygiene increases the risk of bacteraemia following daily activities and IDPs,⁸³ whilst recent data demonstrate that poor oral hygiene and neglected dental health increase the risk of IE in moderate- or high-risk individuals.^{49, 84} Furthermore, although there is clear evidence that both daily oral activities and IDPs cause bacteraemia that could result in IE in susceptible individuals (particularly in the presence of poor oral hygiene or neglectful dental care), there is no clear indication which poses the greater threat and prevention efforts should therefore be directed towards both. Whilst use of AP is clearly impractical to reduce the risk posed by daily oral activities, maintenance of good oral hygiene is likely to reduce the overall risk of OVGS IE and should be used as a preventative measure in all those at moderate- or high-risk of IE.

Non-dental invasive procedures (NDIPs)

Early guidelines encouraged the use of AP before a range of different NDIPs (Table 6) until the mid-2000s, when lack of evidence linking these procedures with subsequent IE combined with wider moves to reduce the use of AP led to withdrawal of these recommendations.^{27, 28} More recently, however, nationwide studies in Sweden and England have demonstrated a significant association between several NDIPs and IE,^{45, 85} prompting reconsideration of the need for AP in this setting. An AHA Scientific Advisory has stated that “there is sufficient evidence associating certain NDIPs with the subsequent occurrence of IE, in particular, in those at high

IE-risk, to warrant a re-evaluation of IE prevention advice”,⁸⁶ while the ESC now provide a Class IIb, level of evidence C recommendation that “systemic antibiotic prophylaxis may be considered for high-risk patients undergoing an invasive diagnostic or therapeutic procedure of the respiratory, gastrointestinal, genitourinary tract, skin, or musculoskeletal systems”.⁶⁹ Further research is required to confirm whether AP has a role in the prevention of IE following NDIPs and determine which procedures pose particular risk.

AP regimens

Since the early 2000’s, there has been near universal agreement concerning the use of single dose oral amoxicillin 30-60mins before IDPs. The risk of ADR is low in patients with no history of penicillin allergy^{54-56, 87} and recent data confirm its effectiveness in reducing IE-incidence.^{33, 47, 48, 88}

Azithromycin (500mg), clarithromycin (500mg), cephalexin (2g), or doxycycline (100mg) have now replaced clindamycin as the first-choice alternative to amoxicillin for patients with a history of penicillin allergy (Table 3).^{54, 87, 89} More data are needed to determine which of these has the greatest efficacy in preventing IE and the lowest incidence of ADRs.

Conclusions

Although the value of IE prevention has always been recognised, associated strategies (particularly AP) have been contentious and controversial. Although a lack of high-quality evidence has plagued the debate and left it open to opinion and conjecture, recent large-scale observational studies are helping to resolve many of the central issues confirming the association between IDPs and IE, and the value of AP. Nevertheless, more needs to be learnt concerning the individual phenotypes at high-risk for IE and the invasive procedures that pose

particular risk. Despite progressive guideline convergence, translation of this consensus to daily clinical practice remains an ongoing challenge.

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Table 1. Cardiac conditions requiring AP prior to invasive dental procedures.^{69, 68}

High-Risk Cardiac Conditions for IE		
Situation	ESC Guidance 2023. ⁶⁹	AHA Guidance 2021. ⁶⁸
Previous IE	AP recommended for patients with previous IE	AP suggested for patients with previous, relapse or recurrent IE
Prosthetic heart valve or repair	AP recommended for patients with surgically implanted prosthetic heart valves	AP suggested for patients with prosthetic heart valves
	AP recommended for patients with transcatheter implanted aortic and pulmonary valve prostheses	AP suggested for patients with transcatheter implantation of prosthetic valves
	AP recommended in patients with any material used for surgical cardiac valve repair	AP suggested for patients with cardiac valve repair with devices, including annuloplasty, rings, or clips
	AP should be considered in patients with transcatheter mitral and tricuspid valve repair	
Congenital heart disease	AP recommended for patients with untreated cyanotic congenital heart disease (CHD)	AP suggested for patients with unrepaired cyanotic congenital heart disease (CHD)
	AP recommended for patients with CHD treated with surgery or transcatheter procedures with post-operative palliative shunts, conduits or other prostheses	AP suggested for patients with CHD treated with surgical or transcatheter pulmonary artery valve or conduit placement such as Melody valve and Contegra conduit
	After surgical repair, in the absence of residual defects or valve prostheses, AP is recommended only for the first 6 months after the procedure	AP suggested for patients with completely repaired CHD with prosthetic material or device, whether placed by surgery or by transcatheter during the first 6 months after the procedure
		AP suggested for patients with repaired CHD with residual defects at the site of or adjacent to the site of a prosthetic patch or prosthetic device
Ventricular assist devices	AP recommended in patients with ventricular assist devices	AP suggested for patients with left ventricular assist devices or implantable heart
Heart transplant	AP may be considered in recipients of heart transplants	AP suggested for cardiac transplant recipients who develop cardiac valvulopathy

Table 2. Procedures requiring AP.^{69, 68}

Situation	ESC Guidance 2023. ⁶⁹	AHA Guidance 2021. ⁶⁸
AP recommended	AP is recommended for patients at high risk of IE undergoing at-risk dental procedures. At-risk dental procedures include: • dental extractions • oral surgery procedures (including periodontal surgery, implant surgery and oral biopsies) • dental procedures involving manipulation of the gingival or periapical region of the teeth (including scaling, and root canal procedures)	AP suggested for all dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth
AP not recommended	AP is not currently recommended in other situations	AP is not suggested for: • Anaesthetic injections through noninfected tissue • Dental radiographs • Placement of removable prosthodontic or orthodontic appliances • Adjustment of orthodontic appliances • Placement of orthodontic brackets • Shedding of primary teeth • Bleeding from trauma to the lips or oral mucosa

Table 3. Recommended AP regimens for high-risk patients undergoing invasive dental procedures.^{68, 69}

Allergy status	Route	Antibiotic	Single dose 30-60 mins before procedure	
			Adults	Children
<u>Not allergic</u> to penicillin or ampicillin	Oral	Amoxicillin	2 g orally	50 mg/kg orally
	IM or IV	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
		Cefazolin or Ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
<u>Allergic</u> to penicillin or ampicillin	Oral	Cephalexin [#] or	2 g orally	50 mg/kg orally
		Azithromycin or clarithromycin or	500 mg orally	15 mg/kg orally
		Doxycycline	100 mg orally	<45 kg, 2.2 mg/kg orally* >45 kg, 100 mg orally
	IM or IV	Cefazolin or Ceftriaxone [†]	1 g IM or IV	50 mg/kg IV or IM

Notes: Aside from one dosage recommendation*, the 2023 ESC and 2021 AHA guidelines are unanimous regarding AP regimens.

IM = intramuscular, IV = intravenous,

[#] Or other first- or second-generation oral cephalosporin at equivalent adult or paediatric dose.

[†] Cephalosporins should not be used in individuals with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

* For children <45 kg, the 2023 ESC guidelines recommend oral doxycycline 2.2 mg/kg,⁶⁹ (whilst the 2021 AHA guideline recommend 4.4 mg/kg).⁶⁸

Table 4. Cardiac conditions at moderate – or intermediate-risk of IE.^{68, 69}

Moderate- or Intermediate-Risk Conditions for IE	
ESC Guidance 2023. ⁶⁹	AHA Guidance 2021. ⁶⁸
Rheumatic heart disease	Moderate- or intermediate-risk patients not defined
Non-rheumatic degenerative valve disease e.g. mitral valve prolapse	
Congenital valve anomalies e.g. bicuspid aortic valve	
Hypertrophic cardiomyopathy	
Cardiovascular implanted electronic devices (CIEDs) e.g. implanted pacemaker or defibrillator	

Table 5. ESC guidelines concerning the use of general preventative measures for patients at moderate- or high-risk of IE⁶⁹

Patients should be encouraged to maintain twice daily tooth cleaning and seek regular professional dental cleaning and follow-up (at least twice yearly in high-risk patients and yearly in others)
Strict cutaneous hygiene, including optimal treatment of chronic skin conditions
Disinfection of wounds
Curative antibiotics for any focus of bacterial infection
No self-medication with antibiotics
Strict infection control measures for at-risk procedures
Discouragement of piercing and tattooing
Limited use of infusion catheters and invasive procedures (wherever possible)
Strict adherence to care bundles for central and peripheral cannulae

Table 6. Historical guidelines for the use of AP prior to invasive procedures

Invasive Procedures	BCS 2004 ⁹⁰	ESC 2004 ¹⁹	AHA 1997 ¹⁸
Gastrointestinal			
Upper GI endoscopy with/without biopsy	✓	-	✓†
Lower GI endoscopy with/without biopsy	✓	-	✓†
ERCP (endoscopic retrograde cholangio-pancreatography)	✓	✓	✓
Colonic surgery	✓	-	✓
Genito-urinary			
Endoscopic prostatic procedures	✓	✓	✓
Cystoscopy and endoscopic urological procedures	✓	✓	✓
Obstetric & Gynaecology			
Caesarean section	✓	-	-
Vaginal delivery	✓	✓§	✓†
Abortion/dilatation and curettage (D&C)	✓	✓§	-
Respiratory			
Bronchoscopic procedures (esp. rigid)	✓	✓	✓
Cardiac			
Implantation of pacemakers/defibrillators	✓	-	-
Percutaneous valve procedures	✓	-	-
Percutaneous coronary procedures/stents	✓	-	-
Coronary artery bypass grafting (CABG)	-	-	-
Coronary angiography		-	-
Otolaryngology			
Tonsillectomy/adenoidectomy	✓	✓	✓
Nasal packing/nasal intubation	✓	-	-
Dermatology			
Skin suturing, drainage or wound management	✓	-	-
Blood transfusion/red cell/plasma exchange	-	-	-
Bone marrow puncture	-	-	-
Dental			
Extractions	✓	✓	✓
Other oral surgical procedures	✓	✓	✓
Scaling of teeth	✓	✓	✓
Endodontic treatment	✓	✓	✓

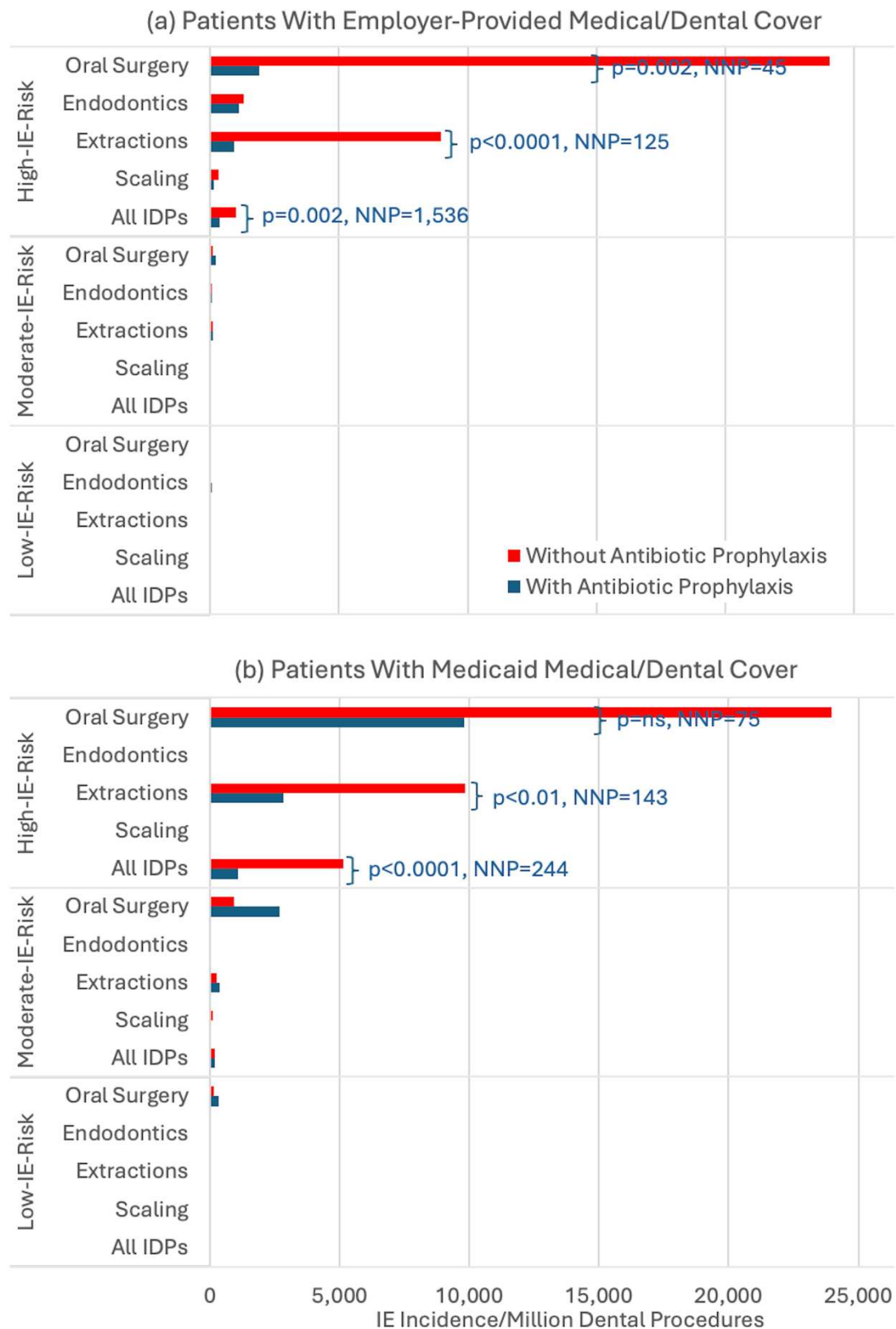
Notes: Invasive procedures for which AP was recommended for moderate- or high-risk individuals by:

(i) the British Cardiac Society (BCS) in 2004,⁹⁰ (ii) the European Society for Cardiology (ESC) in 2004,¹⁹ and (iii) the American Heart Association (AHA) in 1997.¹⁸

Abbreviations/Symbols: TOE = Transoesophageal echocardiography, ✓ = AP recommended, ✓† = the 1997 AHA guidelines listed the recommendation for antibiotic prophylaxis as being optional for high-

risk patients undergoing upper or lower GI endoscopy (with or without biopsy), or vaginal birth delivery,
✓§ = the 2004 ESC guidelines recommended AP for vaginal deliver or abortion/dilatation and curettage
but only in the presence of infection.

Figure 1. Incidence of infective endocarditis (IE) in high-, moderate- and low-risk individuals following invasive dental procedures (IDPs) performed with or without antibiotic prophylaxis.



Legend: Data from US populations with (a) employer provided medical/dental cover,⁴⁷ and (b) Medicaid medical/dental cover⁴⁸ (reproduced with permission from Elsevier and Wiley, respectively). P values compare IE-incidence with and without AP cover (when not shown, p value is insignificant).

Abbreviations: NNP = number needed to prevent (i.e. the number of dental procedures that need AP cover to prevent one IE case), ns = not significant. IE-risk status according to ESC and AHA guidelines.^{68, 69}

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