

P. Moreillon,
for the Swiss Working Group
for Endocarditis Prophylaxis¹

Division of Infectious Diseases,
Department of Internal Medicine
CHUV, Lausanne

Endocarditis prophylaxis revisited: experimental evidence of efficacy and new Swiss recommendations

Summary

Because of its severity, it is agreed that infectious endocarditis should be prevented whenever possible. Determining adequate prophylactic measures involves establishing (a) the patients at risk, (b) the procedures that might provoke bacteraemia, (c) the most effective prophylactic regimen, and (d) a balance between the risks of side effects from prophylaxis and of developing infectious endocarditis. Patients at risk and procedures inducing bacteraemia have been identified by clinical studies. On the other hand, the efficacy of prophylactic antibiotics has been based on animal studies. Randomised, placebo-controlled studies do not exist in humans because they would require large patient numbers and would raise ethical issues due to the severity of the disease. Case-control studies have indicated that infectious endocarditis prophylaxis is effective, but prevents only a limited number of cases.

Animal experiments have revealed several key issues for human application. First, antibiotics do not prevent the early stages of valve colonisation, but rather kill the microorganisms after their attachment to the cardiac lesions. Second, the duration of antibiotic presence in the serum is critical. Under experimental conditions, the drugs must remain above their minimal inhibitory concentration for the organisms for ≥ 10 h, to allow time for bacterial clearance from the valves. Third, antibiotic-induced killing is not the only mechanism allowing bacterial clearance. Other factors, such as platelet microbicidal proteins, may act in concert with the drugs to sterilise the lesions. Recommendations for prophylaxis have recently been revised in Europe and the USA. New information has improved the definition of groups at risk. Since most cases of infectious endocarditis are not preceded by medical pro-

1 Medical societies and coauthors of the Swiss Working Group for Endocarditis Prophylaxis:

Swiss Society of Infectious Diseases:

P. Francioli, CHUV, Lausanne;

R. Malinverni, Hôpital des Cadolles, Neuchâtel.

Swiss Society of Cardiology:

C. Vuille, Hôpitaux Universitaires de Genève;

M. Zuber, Kantonsspital, Luzern.

Swiss Society of Odontostomatology:

M. Perrier, Policlinique dentaire, Lausanne;

J.-P. Carrel, Division de stomatologie et chirurgie orale, CHU, Genève;

J. Samson, Division de stomatologie et chirurgie orale, CHU, Genève.

Swiss Society of Paediatric Cardiology:

F. Stocker, Medizinische Universitätskinderklinik, Berne.

Swiss Society of Paediatrics:

U. B. Schaad, University Children's Hospital, Basel.

Swiss Society of Gastroenterology:

G. Dorta, CHUV, Lausanne;

P. Bauerfeind, Universitätsspital, Zurich.

Swiss Society of Cardiac Surgery:

M. Hurni, CHUV, Lausanne.

Swiss Society of Anaesthesiology:

P. Neidhart, Inselspital, Berne.

Swiss Society of Urology:

P. Jichlinsky, CHUV, Lausanne.

Correspondence:

Philippe Moreillon, MD

Laboratory of Infectious Diseases

CHUV

CH-1011 Lausanne

e-mail: Philippe.Moreillon@chuv.hospvd.ch

cedures, primary prevention of infectious endocarditis should target infected foci responsible for spontaneous bacteraemia (e.g. poor dental hygiene). The purpose of this article is to update the existing recommendations in Switzerland, under the perspective of changing epi-

demiology, the availability of new drugs, and harmonisation with recommendations in other countries.

Keywords: infectious endocarditis; prophylaxis; recommendations; Switzerland

Résumé

Il est généralement admis que l'endocardite infectieuse devrait faire l'objet d'une prophylaxie antibiotique chaque fois que c'est possible. La choix de cette prophylaxie repose sur l'identification (a) des patients à risque, (b) des interventions médico-chirurgicales pouvant provoquer une bactériémie, (c) du régime prophylactique le plus efficace, et (d) du rapport entre le risque d'effets secondaires des médicaments et celui de développer une endocardite infectieuse. Les patients à risque et les interventions médico-chirurgicales provoquant une bactériémie ont été identifiés par des études cliniques. En revanche, l'efficacité de la prophylaxie est fondée sur des résultats chez l'animal d'expérience. Aucune étude randomisée incluant un placebo n'a été effectuée en raison du grand nombre de patients qu'elle nécessiterait et des problèmes éthiques qu'elle soulèverait. Cependant, des études cas-témoins ont démontré que la prophylaxie était efficace dans $\geq 50\%$ des cas. L'expérimentation animale a souligné quelques aspects clés des mécanismes de prophylaxie. Les antibiotiques ne préviennent pas la colonisation des valves par les bactéries, mais éradiquent ces dernières dans un second

temps. Pour ce faire, les médicaments doivent rester pendant une période critique dans le sang: leur taux sérique doit rester pendant au moins 10 h en dessus de leur concentration minimale inhibitrice pour les bactéries cibles. Enfin, l'effet bactéricide de l'antibiotique n'est pas le mécanisme principal de l'éradication bactérienne. Les protéines «microbicides» des plaquettes de l'hôte agissent de concert avec les antibiotiques pour tuer les micro-organismes. Les recommandations pour la prophylaxie ont récemment été réévaluées en Europe et aux Etats-Unis. La plupart des endocardites infectieuses ne sont pas précédées d'une intervention médico-chirurgicale. La prophylaxie primaire doit donc viser le contrôle des foyers responsables de bactériémies spontanées (p. ex. mauvaise hygiène dentaire). Le présent article tente de mettre à jour les recommandations pour la prophylaxie en Suisse, en insistant sur l'épidémiologie changeante de la maladie, les nouveaux antibiotiques à disposition, et l'harmonisation avec les recommandations dans les autres pays.

Keywords: endocardite infectieuse; prophylaxie; recommandations Suisse

Introduction

Ever since Osler has described the microbial origin of infective endocarditis in 1885, cardiovascular infections have remained an area of fascination for both clinicians and medical researchers [1]. The disease was invariably lethal in the preantibiotic era. Depending on the causative pathogen, it can produce a variety of symptoms ranging from acute septicæmia to chronic wasting disease, and thus has been an immense challenge to accurate bedside diagnosis. In the forties, the introduction of penicillin, followed by other antibiotics, revolutionised the treatment and prognosis of infectious endocarditis. Recently, the evolution of clinical microbiology and the availability of new imaging techniques, such as transthoracic and transoesophageal echocardiography, have greatly contributed to set new, more accurate diagnostic criteria [2]. In industrialised countries the improvement in general health care

and the sharp decrease in rheumatic heart disease as a major risk factor have supported the hope of reducing the incidence of the disease. Yet, infectious endocarditis has not disappeared. It rather is on the increase again as reported by recent studies [3–5]. Indeed, new groups at risk have emerged. These include intravenous drug abusers, elderly people with degenerative valve lesions, long-term survivors of complex congenital heart disease, and patients with mitral valve prolapse, valvular prostheses or mechanical devices [6].

Because of its severity, it is agreed that infectious endocarditis should be prevented whenever possible. Determining adequate prophylactic measures entails identifying first the patients at risk, second the procedures that might provoke bacteraemia, third the most adequate antimicrobial regimen, and

fourth the risks of side effects as compared to those of developing infectious endocarditis. In this article we attempt to provide a comprehensive approach to infectious endocarditis prophylaxis based both on the pathophysiology of the disease and on the mechanism(s) of

action of prophylactic drugs. Existing recommendations in Switzerland [7, 8] are reviewed and updated under the perspective of changing epidemiology, the availability of new drugs, and harmonisation with recommendations proposed in other countries [9, 10].

Pathogenesis

The key players in infectious endocarditis are (a) the predisposing factors of the host, (b) the characteristics of the infective microorganism, and (c) the risk of transient bacteraemia.

First, host factors are emphasised by the fact that infectious endocarditis most often develops on preexisting lesions of the endothelial monolayer covering the valve or endovascular surfaces. Normally, this endothelium is very resistant to colonisation and infection by circulating bacteria. However, any lesion of this delicate layer increases the susceptibility to bacterial colonisation by several orders of magnitude. Exposure of the underlying extracellular matrix proteins and the local production of tissue factor trigger the deposition of platelets and fibrin as a normal healing process. Such a platelet-fibrin meshwork, referred to as nonbacterial thrombotic endocarditis, is a perfect nidus for bacterial colonisation during transient bacteraemia [11, 12].

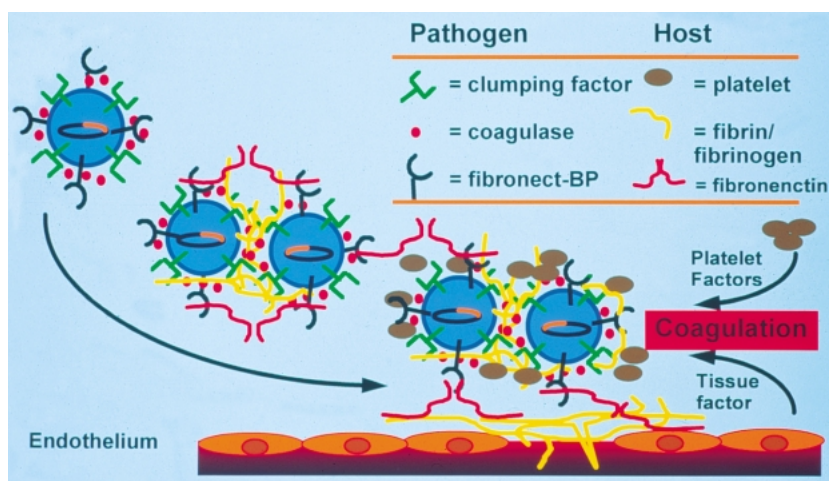
Endothelial lesions may occur in a number of circumstances. Regurgitant valves and congenital cardiac abnormalities, responsible for local turbulent blood stream, may provoke peeling of the endothelium. Likewise, valve remodeling and calcification following rheumatic heart disease or present in sclerotic valves of elderly patients result in endothelial lesions. Finally, extrinsic interventions such as prosthetic valve replacement also promote endothelial damage.

Second, the pathogens most frequently responsible for endocarditis are also those that have the greatest ability to adhere to and colonise damaged valves [13]. Together, *Streptococcus spp.*, *Staphylococcus aureus* and enterococci are responsible for >90% of the infectious endocarditis cases [4, 5]. These organisms also have the greatest capacity to adhere to nonbacterial thrombotic endocarditis in vitro and in vivo [11, 13, 14]. Classical bacteria causing endocarditis are well equipped with surface determinants mediating adherence to valve vegetations. Figure 1 presents a likely scenario in the case of endocardial infection due to *S. aureus*. These organisms possess several surface adhesins mediating attachment to proteins present in the surroundings of endothelial lesions. Fibrinogen-binding protein, or clumping factor, was shown experimentally to be involved in valve colonisation [15]. The role of fibronectin-binding protein, coagulase, and other bacterial adhesins is currently being investigated. In streptococci production of exopolysaccharides is yet another factor promoting adherence to nonbacterial thrombotic endocarditis. Thus, bacteria causing infectious endocarditis possess an abundance of surface determinants, and they might utilise ligand-cooperation to colonise the target tissues.

Third, medico-surgical procedures in nonsterile anatomical sites may provoke transient invasion of the bloodstream with bacteria from

Figure 1

Simplified scenario of colonisation and infection of an endothelial lesion by *Staphylococcus aureus*. (1) Exposure of the subendothelial matrix triggers the deposition of platelet-fibrin clots and other plasma-soluble and matrix proteins, including fibrinogen, fibrin, fibronectin and thrombospondin. Triggering of the coagulation cascade is also mediated by tissue factor, which contributes to platelet activation and constitution of a nonbacterial thrombotic vegetation. (2) *Staphylococcus aureus* are equipped with a wealth of surface determinants that may promote binding and colonisation of nonbacterial thrombotic endocarditis. The best known are fibrinogen-binding protein (or clumping factor), fibronectin-binding protein and coagulase. These factors are likely to mediate direct and/or indirect attachment to vascular lesions and promote infection (see text and references [13, 15]).



the local flora. Such bacteraemia is usually of low grade and of short duration (i.e. less than 100 colony forming units per ml of blood lasting for less than 10 min in the case of dental extraction) [16, 17]. However, depending on the characteristics of the circulating bacteria, such an intervention might put patients with preexisting cardiac lesions at a risk of developing infectious endocarditis. In the case of dental procedures, the post-extraction bacteraemia is more important in patients suffering from gingivitis than in individuals with a healthy gingivo-dental status. This was simulated in rats with catheter-induced aortic nonbacterial thrombotic endocarditis [14]. Animals suffering from periodontitis were at a much higher risk of post-extraction endocarditis than those with healthy gingiva. Most interestingly, while all the rats developed polymicrobial bacteraemia during dental procedure, only one or two types of organisms (i.e.

group-G streptococci and *S. aureus*) produced infectious endocarditis. This correlated well with the ability of these bacteria to attach to nonbacterial thrombotic endocarditis.

It is noteworthy, however, that transient bacteraemia may also occur spontaneously during chewing, tooth brushing and other normal activities. Spontaneous bacteraemia provides a rationale for the fact that most cases of endocarditis are not preceded by medico-surgical procedures. Moreover, since streptococci are normal inhabitants of the mouth, spontaneous bacteraemia during chewing may explain why these bacteria are a predominant cause of endocarditis. Thus, proper prophylactic measures during specific medical interventions will only marginally affect the overall frequency of the disease [18]. Trivial prevention strategies such as good dental hygiene are certainly the best prophylaxis in this context.

Prophylaxis of experimental endocarditis

Although prophylaxis is generally recommended, the rationale for its application is not based on results of randomised, placebo-controlled studies. It would require too many patients and raise unethical issues to complete such an investigation [19]. Antibiotic regimens used in humans thus rely on their proven efficacy to prevent experimental endocarditis in animals.

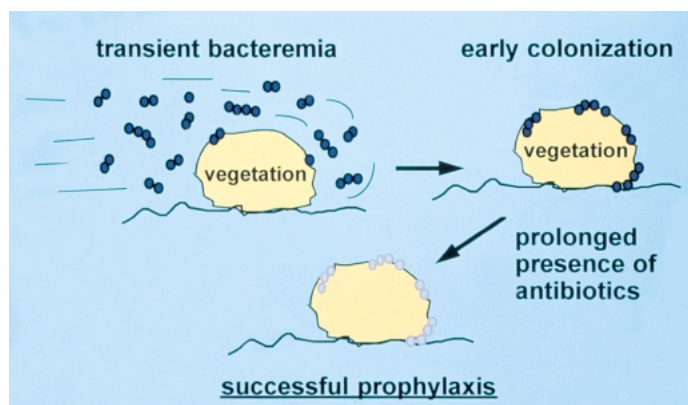
Infectious endocarditis has been modelled in several types of experimental animals. Classically, rats or rabbits with catheter-induced valve lesions are inoculated intravenously with different inoculum sizes of the test organisms, and the development of endocarditis is followed by serial blood cultures and autopsy of the animals. These experiments have allowed the determination of a hierarchy in the infectivity of the pathogens studied. Bacterial adherence was the most critical factor [14].

However, the magnitude and duration of the bacteraemia following inoculation were other important determinants of infectivity [20, 21]. Thus, for a given organism the risk of valve infection was inoculum dependent.

Figure 2 illustrates the *primum movens* of non-bacterial thrombotic endocarditis infection and the principal steps where antibiotic prophylaxis might interfere with the colonisation and infection process. *First* (step 1 in fig. 2), it was thought that antibiotics might shut off transient bacteraemia by killing the organisms either before or while they are circulating in the blood. However, it has been demonstrated that prophylaxis does not reduce the incidence of postprocedure bacteraemia neither in animal experiments [22] nor in humans [16, 17]. The misinterpretation of negative bacteraemia reported in earlier studies was related to the fact that residual drug present in the blood is

Figure 2

Early steps of endovascular infection. (1) Transient bacteraemia may follow a number of trivial circumstances such as chewing and tooth brushing or can be promoted by medico-surgical procedures in nonsterile sites. (2) If valve lesions are present (non-bacterial thrombotic vegetation or nonbacterial thrombotic endocarditis in the figure), the lesions may become colonised by certain types of bacteria, such as streptococci, staphylococci and enterococci, which have an increased ability to stick to nonbacterial thrombotic endocarditis. (3) After colonisation bacteria adherent to nonbacterial thrombotic endocarditis may promote further deposition of platelet-fibrin aggregates and become embedded in the vegetation. This protects the pathogens from cellular host defence mechanisms and leaves them to grow and develop established infection.



not properly inactivated after sampling and antibiotics are carried over into the culture media. This may inhibit bacterial growth and give a false negative result.

Second (step 2 in fig. 2), it was thought possible that certain drugs affecting the bacterial wall, such as β -lactams, might decrease the ability of circulating organisms to stick to and colonise damaged valves. This hypothesis has also been challenged by animal studies [21]. While amoxicillin prophylaxis can indeed decrease bacterial adherence to nonbacterial thrombotic endocarditis in vitro and in vivo, the decrease is very marginal and does not prevent infection. The same study has indicated that successful prophylaxis is due to the prolonged presence of the drug in the serum after the valve has been colonised, rather than to decreased colonisation per se.

Third (step 3 in fig. 2), if bacteraemia and valve colonisation are not impeded by prophylaxis, then successful protection must rely on the ability of antibiotics to eliminate bacteria already attached to the damaged valve. It has been assumed that bactericidal antibiotics are mandatory to achieve this goal [23]. However, further studies have indicated that bacteriostatic drugs can confer successful protection as well, provided that the inoculum size utilised to challenge the animals is not greater than the minimal inoculum infecting 90% of untreated rats (infectious dose 90% or ID₉₀) [24]. When bactericidal regimens are used, successful protection is extended to animals challenged with larger inocula. Nevertheless, such a situation is

unlikely to occur in clinical practice. Indeed, postmanipulation bacteraemia never reaches this level in humans, as indicated by the relative rarity of postprocedure infectious endocarditis.

Several studies have demonstrated that the critical determinant of successful protection is the prolonged presence of the antibiotic in the serum above its minimal inhibitory concentration for the pathogens [25, 26]. The intrinsic bactericidal activity of the drug is of lesser importance. For amoxicillin it has been shown that this duration is ≥ 10 hours. The mechanism by which bacteria adherent to nonbacterial thrombotic endocarditis are killed during this period of time is unclear. Antibiotic-induced killing may be one possibility. In the case of bacteriostatic drugs a dual action of both the antibiotic and intrinsic host factors, such as platelet-microbicidal proteins [27], has been suggested. In practice, prophylactic antibiotics are usually given either in large single doses and/or in repeated doses to ensure their prolonged presence in the serum.

Finally, the fact that bacteria are eliminated after, rather than before colonisation of the valve suggests that prophylaxis might also be effective if given shortly after the procedure. This has been confirmed in animal studies indicating that so-called "postphylaxis" given to rats with catheter-induced nonbacterial thrombotic endocarditis is effective when started for up to 2 hours after bacterial challenge [28]. Beyond this safety window, however, the drug fails to prevent the disease.

Patients at risk

Recommendations for prophylaxis have been established in many countries and experts in the field generally agree on the underlying cardiac conditions that put the patients at risk. However, the exact level of risk of specific lesions is difficult to assess. Some patients are considered to be at especially high risk, due to the higher mortality should an infectious endocarditis occur and to the high incidence of infectious endocarditis related to their cardiac lesion. This is the case for patients with prosthetic valves. Table 1 presents a compilation of the risk groups, modified from the former Swiss recommendations, according to the recent guidelines in Europe and the USA [9, 10]. Some of the risk groups deserve further attention.

Congenital heart disease

Congenital heart disease is a lifelong risk factor, with some exceptions including the successful correction of defects (see below). Congenital heart disease is the most common predisposing lesion in children, found in 75–90% of cases [29], and becomes a more and more prevalent lesion in adults, exceeding 10% in certain series [4, 5, 29]. Congenital heart disease at highest risk are unoperated complex cyanotic lesions, such as transposition of great vessels, double outlet right ventricle or single ventricle (8.2 cases per 1000 patient years), followed by tetralogy of Fallot and ventricular septal defects [30, 31]. The risk of infection in such patients is mainly due to turbulent, high-velocity flow and right-left shunts. Conversely, some lesions carry a very low risk of infectious endocarditis, e.g. atrial septal defect of septum

Table 1

Preexisting conditions associated with an increased risk of developing endocarditis.¹

endocarditis prophylaxis recommended	endocarditis prophylaxis not recommended
high-risk-patients	patients with low risk (close to the risk of the general population)
prosthetic cardiac valves, including bioprosthetic and homograft valves	isolated septum secundum atrial septal defect and sinus venosus defect
previous infectious endocarditis	surgical repair of atrial or ventricular septal defect without residual shunt after 6 months
unoperated complex cyanotic congenital heart disease ²	catheter closure of atrial septal defect without residual shunt after at least 6 months
surgically constructed systemic pulmonary shunts or conduits	surgical or catheter closure of ductus arteriosus without residual shunt after 6 months
moderate-risk patients	mitral valve repair (including with prosthetic ring) 6 months after the intervention (in the absence of residual insufficiency)
operated complex cyanotic heart disease ²	previous coronary artery bypass
other congenital cardiac malformations (except for those specified in the next column)	intracoronary stents
acquired valve dysfunction ³	cardiac transplant (unless valve lesion exists)
hypertrophic obstructive cardiomyopathy	mitral valve prolapse without valve regurgitation
mitral valve prolapse with significant valve regurgitation and/or thickened valve leaflets	functional heart murmur
	previous Kawasaki's disease without valve dysfunction
	previous rheumatic fever without valve dysfunction
	cardiac pacemaker (intravascular or epicardial) and implanted defibrillator

¹ adapted from existing recommendations in Switzerland [7, 8], other European countries [9], and the USA [10]

² including transposition of great vessels, single ventricle, double outlet right ventricle, and tetralogy of Fallot

³ including rheumatic heart disease; see text for details

secundum and sinus venosus defect, cor triatriatum with no or mild obstruction, anomalous pulmonary venous connection, and isolated congenitally corrected transposition of the great arteries [32].

Surgical interventions modify the risk of infectious endocarditis of congenital heart disease in various ways. Complete correction may eliminate or minimise the risk, while palliative surgery may sometimes even increase the risk of infectious endocarditis: this is the case after creation of an aorto-pulmonary shunt or implantation of a mechanical prosthetic valve. Unoperated tetralogy of Fallot and transposition of great vessels are considered as complex cyanotic lesions with a high risk of infectious endocarditis. After operation with no residual shunt such patients are usually classified in the moderate risk group [31, 32]. Surgical closure of an atrial or ventricular septal defect eliminates the risk of infectious endocarditis, provided that no other abnormality exists and no residual shunt is found by colour Doppler echocardiography performed 6 months after the intervention, when sutures and patches should be covered with a new endothelium. Assessing the risk of infectious endocarditis after percutaneous closure of an atrial septal defect is difficult because these devices are still under investigation. Recent information suggests that endothelialisation of such mater-

ial is complete after 6 months (R. Malinverni, personal communication). Antibiotic prophylaxis is thus required for 6 months (some protocols recommend 12 months) after implantation of such devices. Surgical or percutaneous closure of ductus arteriosus eliminates the risk of infectious endocarditis and prophylaxis is not warranted 6 months after the closure in absence of residual shunt. Similarly, after mitral valve repair with a prosthetic ring, prophylaxis of infectious endocarditis is advised only in the first 6 months, i.e. until the ring is fully covered with endothelium in absence of valve incompetence.

Mitral valve prolapse

Mitral valve prolapse carries a risk of infectious endocarditis, which is now well characterised. Previously, problems occurred about the definition of mitral valve prolapse, with some studies reporting prevalence of mitral valve prolapse exceeding 20% [33]. Such series had a wide definition of mitral valve prolapse, including many cases of thin valves with a slight billowing of the leaflet. It is now agreed that, with echocardiography, mitral valve prolapse should be defined as a clear systolic displacement of all or part of a leaflet into the left atrium, in the long-axis view of the left

ventricle. Using such a definition, mitral valve prolapse is found in 4–5% of a general population, and such patients are at risk of infectious endocarditis if their leaflets are thickened and redundant or if the valve is insufficient [34–37]. Thus, only mitral valve prolapse with a systolic murmur of mitral regurgitation, or with a thickened redundant leaflet on echocardiography warrants prophylaxis.

Degenerative valve lesions

Degenerative lesions, including aortic sclerosis, aortic stenosis and mitral regurgitation, are present in up to 25% of patients over 40 and 50% of patients over 60 with established infectious endocarditis, and even more frequently in patients over 70 [38]. Which patients really are at risk of developing infectious endocarditis, remains an issue and the place of prophylaxis is not well defined. For practical reasons prophylaxis is only recommended for patients with a murmur of aortic or mitral stenosis or insufficiency. If echocardiography is performed, patients with at least moderate aortic or mitral stenosis, or mild aortic insufficiency should be classified in the moderate-

risk category. Conversely, patients with aortic sclerosis (mean gradient <10 mm Hg, minimal regurgitation) or with mild mitral, tricuspid or pulmonary regurgitation may not warrant prophylaxis.

Intravenous drug users

The need for prophylaxis in intravenous drug user patients with a history of right-sided infectious endocarditis is uncertain. Right-sided infectious endocarditis is usually of lesser consequence than left-sided infection, the risk of reinfection during medical procedure is not known, and a 2-week course of treatment is generally successful. Prophylaxis is questionable in these individuals. However, prophylaxis may be beneficial in subgroups of these patients suffering from the acquired immunodeficiency syndrome (AIDS), because the risk of death during infectious endocarditis is increased in this population, irrespective of the valve (left-side or right-side) involved [39]. The other situations listed in table 1 are more straightforward, and we refer the reader to additional literature for more details about these issues [7–10].

Procedures producing bacteraemia

Besides normal activities such as chewing and tooth brushing, transient bacteraemia may be induced by a number of procedures performed in nonsterile sites. However, only bacteraemia due to pathogens typically observed in endocarditis is relevant regarding the risk of infectious endocarditis during these interventions.

Dental procedures

The main infectious endocarditis pathogens involved during dental manipulations are viridans group streptococci. Although anaerobic bacteria are the principal organisms released in the circulation during dental procedures [16, 17], they virtually never cause infectious endocarditis and are not the direct target of antibiotic prophylaxis. Moreover, bacteria from the so-called HACEK group (*Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) are found in the mouth, but they are only occasional infectious endocarditis pathogens and less of a concern than streptococci.

There have been questions about what type of dental procedure requires prophylaxis and/or what type of dental treatment should better be avoided in patients at risk. Antibiotics are usually recommended in any event that leads to overt gingival bleeding. Table 2 presents a list of interventions requiring or not requiring antibiotic prophylaxis, as proposed by the American Heart Association [10]. However, patients at risk with poor dental hygiene are at increased risk of bacteraemia. Such individuals might still benefit from prophylaxis even during benign procedures. Local application of antiseptics, including chlorhexidine or iodine-based preparations, may also be beneficial in such individuals, by reducing the inoculum [40]. Some surgical procedures may result in prolonged gingival dehiscence [41]. However, in spite of persisting mucosal breach standard recommendations do not advocate prolongation of antibiotic administration in such circumstances [9, 10].

Two other circumstances deserve further comment. The first concerns procedures that might result in unanticipated bleeding. If prophylaxis has not been given before the intervention, it

Table 2

Dental procedures necessitating or not necessitating prophylaxis in patients at risk.¹

endocarditis prophylaxis recommended	endocarditis prophylaxis not recommended
dental extractions	filling cavities and other restorative dentistry not resulting in bleeding
periodontal procedures such as surgery, scaling, root planing, probing and maintenance	local, non-intraligamentary anaesthetic injections
placement of dental implant and reimplantation of avulsed teeth	placement of rubber dams
root canal instrumentation or surgery beyond apex	postoperative suture removal
subgingival placement of antibiotic fibers or strips	placement or removal of prosthodontic or orthodontic material
initial placement of orthodontic bands (but not brackets)	taking of oral impression (only without retraction)
intraligamentary local anaesthetic injections	taking of oral radiographs
prophylactic cleaning of teeth or implants involving bleeding	fluoride treatment
	shedding of primary teeth

¹ Prophylaxis is indicated in most procedures that result in bleeding of the oral mucosa. Prophylaxis in case of unexpected bleeding or for procedures at low risk performed in heavily infected tissue require further clinical judgement.

Table 3

Other procedures necessitating or not necessitating prophylaxis in patients at risk.

endocarditis prophylaxis recommended	endocarditis prophylaxis not recommended
respiratory tract	respiratory tract
bronchoscopy with a rigid tube	endotracheal intubation
tonsillectomy, adenoidectomy and surgical procedures involving the respiratory mucosa	bronchoscopy with a flexible tube (with or without biopsy)
	tympanostomy tube insertion
gastrointestinal tract ¹	gastrointestinal tract
sclerotherapy/ligation of oesophageal varices	transoesophageal echocardiography ³
oesophageal stricture dilatation	endoscopy with or without biopsy ^{3,4}
endoscopic retrograde cholangiography in case of biliary or pancreatic duct obstruction	
biliary tract surgery	genitourinary tract
surgical procedures involving the intestinal mucosa	caesarean section
genitourinary tract	urethral catheterisation ^{3,5}
prostatic surgery (including biopsy)	uterine dilatation or curettage ^{3,5}
cystoscopy	therapeutic abortion ^{3,5}
urethral dilatation	sterilisation procedures ^{3,5}
vaginal delivery ²	insertion or removal of intrauterine devices ^{3,5}
vaginal hysterectomy ²	circumcision
other	other
implantation of catheter devices for shunt closure	cardiac catheterisation including coronary angioplasty
manipulation of infected areas (e.g. skin abscesses)	implantation of coronary stents, cardiac pacemakers and defibrillators
	incision or biopsy of surgically disinfected skin

¹ Prophylaxis is recommended for high-risk patients; prophylaxis is optional in moderate-risk patients [10].

² Prophylaxis is recommended for high-risk patients, especially those with congenital heart defects (special recommendation of the Swiss Society of Paediatric Cardiology) [66].

³ Prophylaxis is optional for high-risk patients [10].

⁴ There are insufficient data to make firm recommendations in case of polypectomy. Endocarditis prophylaxis is probably not necessary.

⁵ Only if performed in uninfected tissues.

might still be effective if given immediately after the procedure. As already mentioned, the safety window following bacteraemia is about 2 hours in animal experiments [28]. Beyond that, however, prophylaxis might not be effective anymore and administration of antibiotics for a longer period of time might be considered. Second, multiple consecutive interventions may pose a problem if repeated prophylaxis is required. It has been shown that while single-dose amoxicillin prophylaxis is harmless, repeated drug administration selects for streptococcal subpopulations with increased minimal

inhibitory concentrations of the drug in the mouth flora [42]. Such organisms with intermediate to high resistance levels (minimal inhibitory concentration ≥ 1 mg/l) may persist for up to several weeks in the mouth. Multiple procedures should thus be best carried out all at once or separated by more than 8–14 days [10]. While dental manipulations are the most frequent procedures likely to induce streptococcal bacteraemia, the same type of flora must be considered during procedures in other areas of the upper respiratory and digestive tract. These include ear-nose and throat inter-

ventions and bronchial and oesophageal procedures involving bleeding of the mucosa (table 3).

Procedures involving the gastrointestinal and genitourinary tracts

Table 3 presents a number of procedures requiring or not requiring prophylaxis against infectious endocarditis according to existing recommendations [7–10]. Again, the list is only indicative. It does not exclude the administration of prophylaxis in the “not recommended” group when clinical judgement suggests that the manipulated area is infected. Complicated or long-lasting procedures have an increased chance to produce bacteraemia.

During sclerotherapy for oesophageal varices, for example, the risk of bacteraemia increases with the number of sclerosis injections and the size of the needle [43].

Procedures involving the genitourinary and gastrointestinal tracts will mostly produce bacteraemia due to gram-negative bacteria. However, gram-negative bacteria rarely cause infectious endocarditis. Antibiotic prophylaxis is thus primarily aimed at the gram-positive infectious endocarditis pathogen *Enterococcus spp.* in case of such procedures.

Prophylaxis is not recommended in case of vaginal delivery, except if there is overt infection. If complications occur, with prolonged labour or when instrumental delivery is required, antibiotic prophylaxis may be considered.

Prophylactic measures

Primary prevention is essential. This includes providing adequate dental hygiene. We suggest at least one yearly visit to the dentist for all patients at risk of infectious endocarditis. Mouth rinse with antiseptic solutions has been shown effective in this context [42]. Other foci harbouring endocarditis pathogens, such as urinary tract or skin infections, should also be treated. Whenever necessary, antibiotic prophylaxis should target only the most likely endocarditis pathogens potentially released during the intervention.

Dental, oropharyngeal, and oesophageal procedures

Major infectious endocarditis pathogens invading the circulation during such procedures are streptococci. Table 4 indicates the regimen recommended in these situations. A single 3 g oral dose of amoxicillin is standard in many places [9, 41] and ensures a prolonged serum level (≥ 10 h) above the minimal inhibitory concentration for all susceptible streptococci. Some recommendations propose 2 g instead of 3 g, because the serum kinetics produced by both of these regimens is very similar and the lower dosage may produce lesser side effects [10, 44].

In Switzerland amoxicillin is available in packages containing either four 750 mg tablets, or eight 375 mg tablets. To take advantage of this presentation, the revised proposition recommends the following regimen in most of the cases: one oral dose of 2.25 g (3×750 mg)

1 h prior to the procedure, followed by an additional 750 mg tablet (fourth tablet of the package) 6 h after the first dose (table 4). The additional (fourth) 750 mg tablet is optional in moderate-risk patients. This proposition is based on the better efficacy of prophylaxis observed in animals when the presence of the drug in the serum is prolonged [24, 25]. Moreover, using a one-for-all, highly effective regimen will greatly simplify the practical implementation of the recommendations.

For patients allergic to penicillin, clindamycin remains appropriate [7–10]. However, several new drugs, including clarithromycin and azithromycin, have demonstrated efficacy against streptococcal endocarditis in animal experiments [45, 46] (table 4). They are well tolerated and can be taken in single dose because they have a prolonged serum half-life. A single oral dose of cefuroxime axetil (1 g) also produces prolonged drug levels in the serum of humans (≥ 10 h), with acceptable side effects (essentially gastrointestinal) [47, 48]. This dosage was effective in preventing experimental streptococcal endocarditis in rats [49]. Since cephalosporins have a risk of about 10% of cross-allergy with penicillins, they are safe in the majority of penicillin-allergic patients. However, they should not be used in patients with type-1 beta-lactam allergy.

Patients unable to take oral antibiotics should be given the drug intravenously. However, because the presence of amoxicillin and ampicillin in the serum is shorter after i.v. injection than after oral administration, it is proposed to repeat a second injection 6 hours after the

Table 4

Prophylactic regimens in case of oropharyngeal, respiratory and oesophageal procedures.

patient situation	antibiotic	common prophylactic regimens for both moderate-risk and high-risk patients ¹
oral route		
standard situation	amoxicillin ²	<i>adults</i> : 2.25 g (3 × 750 mg) orally 1 h before procedure, plus 750 mg orally 6 h later
		<i>children</i> : 50 mg/kg (maximum 2.25 g) orally 1 h before procedure, plus 15 mg/kg (maximum 750 mg) orally 6 h later
allergic to penicillin	clindamycin ³	<i>adults</i> : 600 mg orally 1 h prior to procedure <i>children</i> : 15–20 mg/kg, maximum 600 mg
	clarithromycin ³ or azithromycin ³	<i>adults</i> : 500 mg orally 1 h prior to procedure <i>children</i> : 15 mg/kg, maximum 500 mg
	cefuroxime axetil ⁴	<i>adults</i> : 1 g orally 1 h prior to procedure
	parenteral route	
standard situation	amoxicillin (or ampicillin)	<i>adults</i> : 2 g intravenously (i.v.) or intramuscularly (i.m.) 30 min prior to procedure, plus 1 g (i.v. or i.m.), or 750 mg orally 6 h later
		<i>children</i> : 50 mg/kg before procedure (maximum 2 g) and 25 mg/kg 6 h later
allergic to penicillin	clindamycin	<i>adults</i> : 600 mg i.v. 30 min prior to procedure <i>children</i> : 15–20 mg/kg, maximum 600 mg
	cefazolin	<i>adults</i> : 1 g i.v. or i.m. 30 min prior to procedure <i>children</i> : 25 mg/kg, maximum 1 g
	vancomycin	<i>adults</i> : 1 g i.v. 1 h prior to procedure, in slow infusion over 1–2 h <i>children</i> : 20 mg/kg, maximum 1 g
	teicoplanin ^{3,4}	<i>adults</i> : 400 mg i.v. or i.m. 1 h prior to procedure

¹ Some of these regimens propose two consecutive doses of antibiotics in order to ensure prolonged serum levels of the drug. The second dose is optional for moderate-risk patients [9, 10].

² Two doses of amoxicillin provide additional protection and take advantage of the drug packaging for adults existing in Switzerland; see text for details.

³ These high doses ensure prolonged drug concentrations in the serum (≥ 12 h for clindamycin and ≥ 24 h for clarithromycin, azithromycin, and teicoplanin). A second dose is therefore not proposed for high-risk patients.

⁴ Because paediatric information equivalent to those for adults are not available for high-dose cefuroxime axetil [47, 48] and teicoplanin, these compounds are not proposed for prophylaxis in children in the present recommendations.

initial dose even in moderate-risk patients (table 4).

Lower gastrointestinal tract and urogenital tract procedures

While most enterococci in Switzerland are susceptible to amoxicillin and ampicillin, the minimal inhibitory concentrations of these drugs (minimal inhibitory concentration = 1 mg/l) are generally higher than those for viridans group streptococci (minimal inhibitory concentration = 0.1 mg/l). Thus, after administration of a similar dose of antibiotic the serum level of the drugs will fall more rapidly below their effective concentration against enterococci than against streptococci. To circumvent this problem, prophylactic drugs against enterococci are given either (a) for a prolonged period (by repeating the doses) and/or (b) as synergistic associations, combining cell wall inhibitors and aminoglycosides.

Table 5 presents the recommendations in this situation.

A new alternative to vancomycin is teicoplanin, which has been shown to be effective in animal experiments [50] and is proposed in the new recommendations for infectious endocarditis prophylaxis in France and the UK [9]. An advantage of this new glycopeptide is its low toxicity [51].

Procedures in other sites

Other situations include surgical procedures at any infected focus susceptible to harbouring infectious endocarditis pathogens (table 6). The drug should cover the most likely bacterium locally present. Skin infection and osteomyelitis essentially involve staphylococci and possibly streptococci. In the case of known or suspected infection due to methicillin-resistant staphylococci vancomycin is the first choice.

Table 5

Prophylactic regimens in case of biliary/pancreatic, lower gastrointestinal and urogenital procedures.

patient situation	antibiotic	regimens for moderate-risk patients	regimens for high-risk patients
oral route			
standard situation	amoxicillin	<i>adults</i> : 2.25 g (3 × 750 mg) orally 1 h before procedure, plus 750 mg orally 6 h later <i>children</i> : 50 mg/kg (maximum 2.25 g) orally 1 h before procedure, plus 15 mg/kg (maximum 750 mg) orally 6 h later	oral route not recommended [9]
allergic to penicillin			refer to parenteral route
parenteral route			
standard situation	amoxicillin (or ampicillin)	<i>adults</i> : 2 g intravenously (i.v.) or intramuscularly (i.m.) 30 min prior to procedure, plus 1 g (i.v. or i.m.), or 750 mg orally 6 h later <i>children</i> : 50 mg/kg before procedure (maximum 2 g) and 25 mg/kg 6 h later	<i>adults</i> : same as moderate-risk, plus gentamicin 1.5 mg/kg i.v. or i.m. within 30 min of starting the procedure, do not exceed 120 mg total dose <i>children</i> : same dosage of gentamicin as in adults, maximum 120 mg
allergic to penicillin	vancomycin	<i>adults</i> : 1 g i.v. 1 h prior to procedure, in slow infusion over 1–2 h <i>children</i> : 20 mg/kg, maximum 1 g	same as above
	teicoplanin	<i>adults</i> : 400 mg i.v. or i.m. 1 h prior to procedure	same as above

Table 6

Prophylactic regimens in case of procedures in infected skin or other foci harbouring infectious endocarditis pathogens.

patient situation	antibiotic	common prophylactic regimens for both moderate-risk and high-risk patients ^{1,2}
not allergic to penicillin		
oral route	flucloxacillin	<i>adults</i> : 2 g orally 1 h prior to procedure, plus 500 mg orally 6 h later <i>children</i> : 30 mg/kg before procedure (maximum 2 g) and 15 mg/kg (maximum 750 mg) 6 h later
	cefuroxime axetil ³	<i>adults</i> : 1 g orally 1 h prior to procedure
parenteral route	flucloxacillin	<i>adults</i> : 1 g i.v. or i.m. 30 min prior to procedure, plus 1 g i.v. or i.m. or 500 mg orally 6 h later <i>children</i> : 25 mg/kg (maximum 1 g) i.v. or i.m. 30 min prior to procedure, plus 25 mg/kg (maximum 1 g) i.v. or i.m. or 15 mg/kg (maximum 750 mg) orally 6 h later
allergic to penicillin		
oral route	cefuroxime axetil ³	<i>adults</i> : 1 g orally 1 h prior to procedure
parenteral route	cefazolin	<i>adults</i> : 1 g i.v. or i.m. 30 min prior to procedure <i>children</i> : 25 mg/kg (maximum 1 g) i.v. or i.m. 30 min prior to procedure
	vancomycin	<i>adults</i> : 1 g i.v. 1 h prior to procedure, in slow infusion over 1–2 h <i>children</i> : 20 mg/kg (maximum 1 g) i.v. 1 h prior to procedure, in slow infusion over 1–2 h
	teicoplanin ³	<i>adults</i> : 400 mg i.v. or i.m. 1 h prior to procedure

¹ Some of these regimens propose two consecutive doses of antibiotics in order to ensure prolonged serum levels of the drug. The second dose is optional for moderate-risk patients [9, 10].

² If methicillin-resistant *Staphylococcus aureus* or methicillin-resistant coagulase negative staphylococci are suspected, the most adequate regimen is vancomycin as specified above. Teicoplanin might be considered as alternative against MRSA.

³ Because paediatric information equivalent to those for adults are not available for high-dose cefuroxime axetil [47, 48] and teicoplanin, these compounds are not proposed for prophylaxis in children in the present recommendations.

Prophylaxis of nonvalvular endovascular infections

Nonvalvular endovascular infections primarily involve permanent intravascular devices, such as catheters and pacemakers, as well as prosthetic vascular grafts. In the majority of cases infection results from perioperative contamination with bacteria from the skin [52, 53]. Coagulase negative staphylococci and *S. aureus* are most commonly involved. Haematogenous graft infection is anecdotal. In one retrospective study of 41 patients with late (1–224 months after operation) prosthetic

graft infections most cases resulted from bacterial implantation at the index operation [54]. Only 2 cases were compatible with haematogenous seeding. While antibiotic prophylaxis is thus often given at the time of operation, secondary prophylaxis is usually not recommended. Instead, recent research has been aimed at modifying the device surfaces to hamper bacterial colonisation and/or growth rather than at promoting general antibiotic therapy.

Cost-benefit of infectious endocarditis prophylaxis, an as yet incompletely solved issue

Since there exists no prospective study assessing the efficacy of antibiotics in preventing infectious endocarditis, the precise efficacy of this prophylactic strategy in humans is unknown. Several population-based analyses have shown that infectious endocarditis patients with both a known predisposing heart condition and an identifiable procedure prone to bacteraemia represent only 8–15% of all patients presenting with infectious endocarditis [54–56]. Moreover, several failures of prophylaxis have been reported [57], suggesting that certain antibiotics, e.g. erythromycin, can fail to provide protection. Thus, from a public health point of view antibiotic prophylaxis will only prevent a limited number of cases.

The efficacy of antibiotic prophylaxis has been evaluated by several population-based studies. The first published study looked at patients with prosthetic valves who underwent a risk procedure with or without an adequate antibiotic prophylaxis: endocarditis was diagnosed within 14 days after the procedure in 6/390 procedures without prophylaxis compared to 0/287 procedures with antibiotics [58]. Two population-based case-control studies of patients with either native valve infectious endocarditis only or native and prosthetic valve infectious endocarditis have estimated that the protective efficacy of antibiotics was 49 and 46% respectively [18, 59].

One study has found an efficacy of 91%, but suffers from several potential biases [60]. Because of the rarity of the disease, the small proportion of cases which could potentially be prevented and the limited efficacy of antibiotics, the authors of one of these studies calculated that antibiotic prophylaxis would prevent only about 5 cases per year in the Netherlands (14.5 million inhabitants) [17]. A recent study in the USA has also strongly challenged the usefulness of endocarditis prophylaxis in a population-basis analysis [61]. From their data the authors concluded that even if 100% effective prophylaxis would reduce the incidence of infectious endocarditis only by 2.0 cases per 1 000 000 person years. Nevertheless, the association between dental extraction in patients with previous valve lesion and increased risk of endocarditis remained true in this study.

These data suggest that antibiotic prophylaxis may be worthwhile for the individual patient but its effect on the whole population is negligible. Thus, while they do not challenge the indication for prophylaxis in selected patients, they underline the fact that from a public health point of view the situation might be less clear-cut. The cost for one case prevented has been estimated to be 2.6 million US\$ with 2 days of oral penicillin [62] and 600 000 US\$ for oral erythromycin [63]. This highlights the importance of carefully selecting the patients who will mostly benefit from antibiotic prophylaxis [64] and dampens the enthusiastic overuse of this prevention strategy. Clearly, continuing studies on this issue are required.

Conclusion

The revised recommendations outlined above are based on (a) existing evidence of drug efficacy in animal models of infectious endocarditis, (b) the review of the recent literature, and (c) the recommendations existing in other industrialised countries. The present propositions were elaborated, reviewed and accepted by representatives of the Swiss medical societies listed in the authorship. They should be used as guidelines, because they cannot address all specific cases and might have to be adapted in certain individual patients.

Since most of the cases of infectious endocarditis are not preceded by medico-surgical procedures, antibiotic prophylaxis in patients at risk will prevent only a small proportion of cases. For this reason the cost-benefit advantage of prophylaxis has been questioned [18, 61–63]. However, preventing even a small number of cases seems desirable, because the morbidity and cost of established infectious endocarditis is very high [19]. Adequate selection of patients requiring prophylaxis is an issue. It is the role of the healthcare provider to target on the right population and to avoid overuse of antibiotics, which may result in increased costs and side effects and promotes the emergence of bacterial resistance against antibiotics used for infectious endocarditis prophylaxis [65].

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