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Efficacité de l'antibioprophylaxie chirurgicale

Timkapon, Daniel

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Effcacité de l'Antibioprofylaxie Chirurgicale

Dr. Daniel Timkapon

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List of abbreviations

AB	Antibiotic
APC	Antibioprophylaxie chirurgicale
ASA	American Society of Anesthesiologists
CABG	Coronary artery bypass graft surgery
CDC	Centre for disease control and prevention
EVD	Extra ventricular device
GEP	Gastrotomie endoscopique per cutanée
GNB	Gram negative bacteria
ISO	Infection du site opératoire
MRSA	Meticillin-resistant streptococcus aureus
NNISS	National Nosocomial Infections Surveillance System
PVVS	Personne vivant avec le virus du SIDA
QDC	Quebec Drug Council
RCT	Randomized controlled trials
RTUP	Résection transurethrale de la prostate
SAP	Surgical antibiotic prophylaxis
SARF	Society of anesthesia and Resuscitation of France
SSI	Surgical Site Infection
TURP	Transurethral resection of the prostate.
UHG	University Hospital of Geneva

Résumé en français

Introduction

La prévention des infections du site opératoire (ISO) est une priorité de santé publique.¹ Plusieurs études contrôlées ont démontré le bénéfice de l'antibioprophylaxie chirurgicale (APC) dans la prévention des ISO. L'APC est de ce fait devenue une pratique de routine largement répandue à travers le monde. Un tiers des antibiotiques prescrits en milieu hospitalier dans le monde est consacré à la prévention des ISO.² Plusieurs enquêtes menées dans divers continents rapportent pourtant que l'incidence des ISO reste aussi élevée qu'avant l'adoption de l'APC comme pratique de routine.³⁻⁵ Le taux d'incidence actuel des ISO varie entre 16.9% et 38%.⁶⁻⁹ De plus, les septicémies post chirurgicales restent, par leur fréquence, un problème important dans le monde.¹⁰ Selon une étude menée en Suisse, l'incidence des ISO dans ce pays était de 5.6% en 2002, avec 38% de décès attribuable.¹¹ Doit-on en conclure que l'APC est inefficace? Les normes de l'APC sont-elles bien exécutées en pratique quotidienne sur le terrain? Quelle est la pertinence et la valeur scientifique des résultats publiés par les études sur l'efficacité de l'APC ? Les réponses à ces questions nous permettront de comprendre pourquoi les ISO restent aussi fréquentes, alors que l'APC est largement pratiquée. Nous avons trois objectifs spécifiques:

- Résumer et discuter les principales trouvailles des audits sur la mise en oeuvre des normes et principes de l'APC.
- Faire une revue des études contrôlées qui comparent l'efficacité de l'APC versus placebo, dans la prévention des ISO et commenter leurs conclusions.
- Recommander des mesures correctrices permettant d'améliorer la qualité et l'efficacité de l'APC, pour ainsi réduire l'incidence des ISO.

Première partie

Infection Du Site Opératoire : Identification, Étiologies et Facteurs de Risque

Introduction

L'APC vise à réduire la prolifération microbienne au sein du site chirurgical, afin de diminuer les

risques d'infection postopératoire. La surveillance des ISO implique de pouvoir les reconnaître par quelques caractéristiques cliniques et épidémiologiques.

Identification des ISO

L'ISO est un processus infectieux localisé, qui survient du fait de l'effraction de la peau, avec invasion des tissus et des organes. L'ISO résulte de la contamination des tissus sains par les micro-organismes, et se manifeste dans les 30 jours qui suivent l'intervention chirurgicale.

Etiologies

Les germes le plus souvent mis en cause dans l'étiopathologie des ISO sont des bactéries ou des champignons. La bactérie la plus fréquente, selon Andrajati et al,²⁵ est *Staphylococcus aureus* avec 90,8% des cas, et le champignon le plus retrouvé, d'après l'étude de Mc Neil et al,²⁹ est *Candida albicans*.

Les facteurs de risque

Plusieurs facteurs de risque peuvent favoriser la survenue d'une ISO. On distingue : les facteurs de risque liés aux germes (virulence, concentration de l'inoculum et pouvoir pathogène); les facteurs de risque liés aux patients (statut immunitaire, obésité,⁴⁰ tabagisme³⁷⁻³⁹); les facteurs de risque liés à la chirurgie (hygiène chirurgicale); et les facteurs de risque liés à l'environnement.

Conclusion

Les caractéristiques des ISO sont bien définies et doivent être prises en compte. Une évaluation soigneuse des facteurs de risque doit être faite au moment de déterminer l'indication d'une l'APC.

Deuxième partie

Evaluation de la mise en oeuvre des principes fondamentaux de l'antibioprophylaxie chirurgicale (APC).

Matériel et méthodes

Ce chapitre récapitule et discute les trouvailles des études qui évaluent la façon dont les normes de l'APC sont exécutées dans les blocs opératoires. La bonne exécution de ces normes est un indicateur d'adéquation.

Stratégie de recherche

Des études ont été identifiées et sélectionnées dans la base de données "Cochrane library", en utilisant des mots clefs appropriés.

Critères d'inclusion

Etaient pris en compte, les études cliniques prospectives, évaluant la mise en œuvre des normes de l'APC chez des patients opérés. Ces normes s'expriment sous la forme de cinq grands principes : 1- Introduire l'APC seulement après avoir posé une indication claire ; 2- Bien choisir l'antibiotique à utiliser, en fonction du type de chirurgie et de l'écologie bactérienne locale ; 3- Respecter les dosages recommandés ; 4- Respecter le timing d'administration des antibiotiques ; 5- Respecter la durée d'administration recommandée.

Critères d'exclusion

Ont été exclus : Les études rétrospectives ; les études basées sur des questionnaires ; Les méta-analyses.

Synthèse et extraction des données

Le taux d'exécution inadéquate d'une norme donnée de l'APC est un indice. L'ensemble des indices permet de mesurer l'adéquation globale de l'APC. Ces indices sont extraits de chaque étude consultée. Les indices liés au choix de la technique, à l'hygiène chirurgicale et à l'environnement dans lequel l'intervention chirurgicale se déroule ne sont pas pris en compte. Les cinq indicateurs d'une APC inadéquate sont respectivement désignés par les indices R1 : APC non indiquée ; R2 : Antibiotique mal choisi ; R3 : Dose inappropriée ; R4: Mauvais timing ; R5: Durée inappropriée et R6 : Inadéquation globale. Ces indicateurs sont exprimés en pourcentage. Ainsi, quand par exemple, dans une étude, il est indiqué que 10% des patients ont eu droit à une APC alors que celle-ci n'était pas indiquée, nous notons l'indice R1=10%.

Analyse statistique

Les données collectées sont analysées à l'aide du logiciel Microsoft Excel 2003. Chaque indicateur de mauvaise pratique est considéré comme valable et pris en compte pour une étude donnée quand $R > 20\%$. Nous avons considéré $R < 20\%$ comme un indicateur de bonne pratique.

Résultats

Trente études répondant aux critères d'inclusion ont été recueillies, incluant au total 28.822 patients. Nous avons retrouvé $R1 > 20\%$ dans 8 études sur 10 (80%) ; $R2 > 20\%$ dans 9 études sur 17 (52.9 %) ; $R3 > 20\%$ dans 5 études sur 13 (38.4%) ; $R4 > 20\%$ dans 5 études sur 20 (25 %) ; $R5 > 20\%$ dans 12 études sur 21 (57.1%) ; et $R6 > 20\%$ dans 18 études sur 20 (90%).

Discussion

Indication de l'APC

La chirurgie moderne dramatise les ISO. Les chirurgiens évitent cette complication de plus en plus difficile à justifier et à expliquer aux patients. L'éviction des problèmes médico-légaux que pourra engendrer une ISO grave et inattendue prend ainsi le pas sur les critères scientifiques posant ou réfutant l'indication d'une APC. Nos résultats démontrent aussi une tendance à l'empirisme et à la systématisation. Plusieurs audits démontrent également que l'indication de l'APC n'est pas toujours clairement posée.⁷¹⁻⁷³ Or, une APC injustifiée augmente la pression de sélection des micro-organismes et favorise l'apparition des germes résistants, ceci explique en partie la fréquence trop élevée des ISO. Même judicieusement employé, l'antibiotique est susceptible de provoquer des modifications de la flore bactérienne endogène du tube digestif, de la peau et des muqueuses et induire des résistances,⁷⁴⁻⁷⁷ ce qui contribue aussi à augmenter la fréquence des ISO.

Choix de l'antibiotique

Un choix judicieux et approprié de l'antibiotique à utiliser tient compte de l'écologie bactérienne du milieu et du type de chirurgie à exécuter. Les recommandations en la matière sont basées sur ces critères. Une évaluation préalable des facteurs de risques doit être faite.⁷⁸ Plusieurs études menées en Europe, dont celle de Gilles et al⁵² démontrent que les antibiotiques utilisés pour l'APC ne sont généralement pas conformes aux recommandations en vigueur. Cet auteur constate que les chirurgiens sont réticents à choisir les antibiotiques recommandés par les Guidelines mises à leur disposition. Ils préfèrent se fier à leur propre expérience. La trop grande disponibilité des

médicaments favorise aussi une utilisation abusive. Evidement, les conséquences sont les mêmes que ceux décrites dans le paragraphe précédant.

La détermination de la Dose

Les erreurs portant sur le dosage de l'antibiotique sont très fréquentes, mais cet indicateur ne semble pas avoir une grande incidence sur la prévention des ISO. Des études comparant les résultats obtenus avec une dose unique d'antibiotique à ceux obtenus avec des doses multiples n'ont pas montré une différence significative.⁸³⁻⁸⁸

Le Timing

Il existe une relation étroite entre le timing de l'APC et son efficacité. Ce facteur est essentiel pour la prévention de l'ISO. L'antibiotique doit en effet être présent dans les tissus du patient au moment de la contamination bactérienne. Il doit de ce fait, être administrée quelques minutes avant le début de l'intervention chirurgicale, généralement au moment de l'induction anesthésique.¹⁰⁰⁻¹⁰³ Des études contrôlée ont montré que l'ont parviens à réduire de manière significative l'incidence des ISO en administrant l'antibiotique dans l'intervalle de deux heures qui précède le début de l'intervention. Un mauvais timing réduit évidemment l'efficacité de la prévention.

La Durée

Cette étude démontre qu'une APC anormalement longue constitue la plus importante source d'erreur. Selon les recommandations internationales, l'antibiotique ne doit pas être administré sur une période excédant 48 Heure.⁴⁹ Prolongée au delà de la fermeture de la plaie opératoire, l'APC est sans bénéfice supplémentaire.^{104,111-116}

Conclusion

Notre étude montre que les normes de l'APC sont globalement mal exécutées, d'où la réduction de son efficacité et la trop grande fréquence d'ISO.

Troisième partie

Meta- analyse des études contrôlées comparant l'APC au placebo pour la réduction de l'incidence des ISO

Matériel et méthode

Ce chapitre est une méta-analyse des principales études randomisées qui comparent l'efficacité de l'APC versus placebo dans la prévention des ISO chez les patients traités chirurgicalement.

Stratégie de recherche

Toutes les études contrôlées comparant l'APC versus placebo ont été colligées dans la base de données "Cochrane library" en utilisant les termes appropriés.

Analyse statistique

Les données ont été analysées au moyen des logiciels Microsoft Excel 2003, puis Revman 5.0 associé à la méthode de Mantel-Haenszel à effet fixe. Le chi-carré a permis de calculer les ratios. La valeur seuil $P < 0.05$ était considérée comme statistiquement significative. L'effet funnel plot a servi à la détection des biais de publication.

Résultats

Quarante et une études contrôlées, incluant au total 8280 patients, ont été sélectionnées parmi les 914 retrouvées dans la littérature et regroupées en 7 méta-analyses. Les études sélectionnées étaient publiées entre 1978 et 2007, dans 20 pays différents, et principalement aux Etats-Unis d'Amérique (26.8%), aux Pays Bas (12.2%) et aux Royaumes unis (9.8%). Chacune des 7 méta-analyses de cette étude a montré une efficacité supérieure de l'antibiotique sur le placebo, dans la prévention des ISO, la différence étant chaque fois statistiquement significative.

Discussion

Le choix de l'antibiotique

Les antibiotiques choisis par nos auteurs étaient généralement adaptés et répondaient à l'écologie bactérienne locale. Nous avons cependant retrouvé une étude dont le protocole ne spécifiait pas l'agent antimicrobien à utiliser. Les chirurgiens ayant participé à cette étude ont donc chacun librement choisi un antibiotique donné, dans 124 interventions au total. Au delà de l'incidence sur la valeur scientifique des résultats obtenus, Ceci pose un problème de productivité.

Hygiène chirurgicale et APC

Il a été établi que 90 % des sites opératoires contiennent des germes pathogènes, au moment de leur fermeture, quelques soit les mesures prises au cours de l'intervention.¹⁵⁷ Il faut donc en déduire que la prévention des ISO est pour une part très importante, tributaire de l'APC. On sais aussi que l'application stricte des ces mesures d'hygiène permet de prévenir efficacement les ISO. Seule 3 études ont précisé que des mesures hygiéniques strictes avaient été prises pour réduire leur influences sur les résultats.^{159,84,134} Par conséquent, nous ne pouvons pas rationnellement exclure le nombre d'ISO qui pourrait avoir été provoqué par des mesures d'hygiène insuffisantes.

Surveillance des ISO

Eriksen et al¹⁶⁰ a prouvé que la plupart des infections des ISO sont diagnostiqués après que les patients soient sortis de l'hôpital. Dans l'une des études incluses dans notre revue, l'auteur dit n'avoir suivi les patients que jusqu'au 7ème jour postopératoire. La plus part de nos auteurs ont téléphoné aux patients en phase post hospitalière pour leur demander s'ils avaient eu une ISO ou pas. Ainsi, nous pensons que ces études ont pu donner des valeurs surestimées de l'incidence des ISO. En effet, chaque patient peut bien se méprendre devant des symptômes subjectifs d'un phénomène inflammatoire, entrant dans le cadre d'une cicatrisation normale qu'il prendrait pour une ISO. Cette inquiétude est partagée par Whitby et al.¹⁶² Une ou plusieurs consultations de control en ambulatoire permettraient d'obtenir des résultats plus crédibles.

Etiologie des ISO

Le rôle du MRSA est bien défini. La contamination du site opératoire survient le plus souvent après l'intervention. On incrimine les soins post opératoires. Ce germe est trop souvent déjà présent sur la peau et les muqueuses du patient au moment de son admission à l'hôpital. Sankar et al ¹⁶⁶ montre qu'un dépistage systématique du MRSA réduit significativement l'incidence des ISO. Aucun de nos 41 auteurs n'a systématiquement dépisté le MRSA chez les patients inclus dans son étude. Les soins post opératoires ne sont pas non plus décrits. Dès lors, peut-on affirmer que la qualité des soins post opératoires n'ont pas influencé les résultats publiés par études ?

Infections fongiques

Plusieurs de nos auteurs (14 sur 41) n'ont pas recherché une infection fongique dans le bilan étiologique des cas d'ISO observées. Aucun des traitements prophylactiques n'a utilisé un

antifongique, et pourtant, on sait que les antibactériens n'ont pas tous une action antifongique. On en déduit que les patients n'ont forcement pas été tous bien couvert par l'APC.

Infection à HIV

Dans notre revue, 3 études sur les 41 n'ont pas exclu des PVVS. Cette omission assurément a pu affecter leurs résultats. En effet, Boukinda et al,¹⁷⁰ a montré que 20, 9% de patients traités par chirurgie sont des personnes vivant avec le virus du SIDA (PVVS). Martinson et al¹⁷¹ pour sa part a retrouvé 32.8% de PVVS. Pan et al¹⁶⁹ a montré que les PVVS ont un risque accru d'ISO par rapport à la population normale. Pour cette raison, une étude qui évalue l'efficacité de l'APC devrait exclure les PVVS.

Le tabagisme

13 auteurs sur 41 n'ont pas formellement exclu des fumeurs, or, on sait que les fumeurs sont plus susceptibles de faire une ISO que les non fumeurs. Kamath et al¹⁵⁵ a suffisamment mis en exergue, le rôle du tabac en tant facteur de risque d'ISO.

Les cures de Hernie avec prothèse

La plupart des études de cette revue, pris individuellement n'ont pas pu établir que l'efficacité de l'APC était supérieure à celle du le placebo dans la prévention des ISO. Sur 120 patients opérés pour une cure de hernie inguinale avec insertion de prothèse sous APC, Yerdel et al¹¹⁹ n'a obtenu aucune ISO. Aucune preuve scientifique n'est à ce jour, en faveur d'une APC systématique pour cette intervention particulière.

La Chirurgie dentaire

L'utilité de l'APC en chirurgie dentaire demeure discutable. Cette pratique, qui ne repose sur aucun support scientifique est encore empirique mais rependue aux Etats-Unis ou, selon Yingling et al,¹⁷² 37% de chirurgiens la pratiquent. Notre méta-analyse établie cependant une différence d'efficacité significativement supérieure de l'APC sur le placebo. On ne peut donc recommander que L'APC soit systématiquement prescrite ici.

La Césarienne

Selon les recommandations des guidelines, l'administration systématique d'un gramme de Cefazoline en IV après le clampage du cordon ombilical est efficace. Une étude récente a démontré que les résultats sont meilleurs lorsque cet antibiotique est administré en début d'intervention,¹⁷³ ce qui est infirmé par l'étude de Wax's et al.¹⁷⁴ La première option nous paraît préférable, car elle protège le fœtus.

La Résection transurethral de la prostate

Des études ont montré que l'APC n'est pas nécessaire dans la RTUP. Scholz et al.¹⁷³ démontre qu'un gramme de ceftriaxone en IV prévient efficacement les ISO. Il faut également considérer que ce type d'intervention est généralement pratiqué sur des personnes âgées, trop souvent sujettes aux associations morbides, ce qui, évidemment, augmente les risques d'ISO

La Gastrotomie endoscopique percutanée

En dehors des ISO, d'autres types d'infections, peuvent survenir après une GEP, en particulier : les pneumonies et les péritonites. Les patients ayant bénéficiés d'une GEP sont également sujets aux septicémies fongiques¹⁷⁶

L'Hystérectomie

Dans l'étude de Cubillos¹⁵¹ l'efficacité du Tinidazol oral, administré simultanément avec l'association Myconazol-tinidazol intra vaginal est évaluée, chez des patients bénéficiant d'une hystérectomie. Cubillos travaille avec des patientes ayant déjà reçu la Cefazoline intraveineuse en préopératoire, dans les deux groupes. Quel est l'apport de la Cefazoline que chaque patient a reçu au début de l'expérience ? Quel est le bénéfice de l'Imidazole additionnel dans la prévention des ISO ? Le SARF recommande 2 grammes de Cefazoline en dose unique préopératoire. Le Conseil Québécois du médicament recommande quand à lui 1 gramme de Céfazoline IV.¹⁷⁸ Les ISO sont plus fréquentes dans des hystérectomies par voie vaginales que dans celles par voie abdominales (6% 25% contre 4% à 10%). Nous recommandons donc une APC systématique dans l'hystérectomie vaginale mais pas dans l'hystérectomie abdominale.

Chirurgie orthopédique et traumatologique

La chirurgie orthopédique et traumatologique comporte un très grand risque d'ISO.¹⁸⁰ L'APC est d'emblée systématique, associée aux mesures hygiéniques très strictes. L'intérêt des deux études que nous avons retrouvées est d'étudier le bénéfice additionnel qu'une APC topique et locale peut apporter à la prévention des ISO. Nous avons démontré une différence fortement significative en faveur de l'APC. La prévention d'une contamination du site opératoire par les germes du vestibule nasal est ainsi mise en évidence.

Conclusion

Le but de cette thèse était d'essayer d'expliquer pourquoi le taux de SSI est très élevé. Cette revue a établi une corrélation entre une mise en pratique inadéquate des normes de l'APC et les probables répercussions sur son efficacité. Les résultats disponibles en littérature chirurgicale ne reflètent pas toujours la réalité, en raison des problèmes liés à la méthodologie et aux biais de publication. Ces résultats sont parfois surestimés, et parfois sous-estimés. L'APC reste une mesure efficace, mais pas suffisamment, comparé aux potentialités que cette mesure préventive revêt.

Recommandations

Au terme de cette étude, les recommandations suivantes peuvent être émises :

1- Décourager la pratique l'APC sans évaluation complète des risques d'ISO. Eviter les associations inutiles de plusieurs agents antimicrobiens. 2- Améliorer l'observance des recommandations, et en particulier, en ce qui concerne le timing et la durée d'administration des antibiotiques 3- Décourager l'utilisation abusive des antibiotiques. 4- Tenir compte des infections fongiques, particulièrement chez les patients immuno-compromis. 5- Améliorer la surveillance des ISO chez les patients ayant quitté l'hôpital. 6- Procéder à un dépistage systématique du MRSA à l'admission des patients.

Abstract

Background

Routine use of surgical antimicrobial prophylaxis (SAP) is well-established, but the incidence rate of surgical site infection (SSI) remains high. Does this mean that surgical antimicrobial prophylaxis is not effective?

Objectives

This thesis investigates why the incidence rate of SSI remains high, despite extended SAP practice. We examined the correlation between inappropriateness of the SAP practice and its effectiveness. Subsequently, we discuss the findings of trials that compare patients receiving surgical antimicrobial prophylaxis to those receiving placebo. Finally, we recommend some measures to reduce the incidence rate of SSI.

Methods

The thesis consists of two complementary investigations. Studies that audit the appropriateness of SAP practice were selected from the Cochrane library databases. The collected data were analyzed using Microsoft Excel 2003. Randomized controlled trials (RCT) comparing antibiotics versus placebo were also selected from the Cochrane Library database. Data were analyzed using Microsoft Excel 2003 and Revman 5.0.

Results

The overall SAP practice was inappropriate in 18 (90 %) of the 20 studies that evaluated the global appropriateness of SAP. Forty-one RCT were grouped into seven surgical types. The All the seven groups presented a statistical superior benefit of antibiotics to placebo.

Conclusion

Inappropriate SAP practice seems to explain the very high incidence rate of SSI.

Introduction

Prevention of surgical site infection (SSI) is a public health priority.¹ Several randomized controlled trials (RCT) have shown significant evidence to prove the benefit and efficacy of surgical antimicrobial prophylaxis (SAP) in SSI prevention. Consequently, routine SAP to prevent postoperative infection has become a well-established practice all over the world. SAP represents approximately one-third of the hospital antimicrobial prescription.² Despite this, the incidence rate of SSI has been reported by many authors to remain high.³⁻⁵ In the literature, the current reported incidence rate of SSI is higher than that which was known before the routine use of prophylactic antibiotics. Indeed, the high current SSI incidence ranges from 16.9% to 38%,⁶⁻⁹ meanwhile, post-surgical sepsis continues to be a significant problem across the globe.¹⁰ A Swiss study showed an incidence rate of SSI of 5.6% in 2002, with 38% of attributable death.¹¹ It is therefore evident that efforts have to be made in order to reduce the incidence rate of SSI. One field of research consists of examining the principles of SAP, as well as their appropriate implementation within surgery. One important aspect is that of the relevance of the results of current trials on the efficacy of SAP compared to placebo therapy in preventing SSI. The aim of this thesis is to investigate why the incidence rate of SSI is still high. Specific objectives are:

To review, summarize and discuss the main findings of studies about the appropriateness of antibiotic prophylaxis principles in common surgical procedures.

To review randomized control trials on prophylactic antibiotic (AB) compared to placebo therapy in the reduction of incidence rate of SSI, and to comment on their findings.

To recommend comprehensive and feasible corrective measures that may help to reduce the incidence rate of SSI.

Part I

Surgical site infection: A review of the Identification, Aetiology and Risk factors

I- 1 Introduction

The goal of antimicrobial prophylaxis in surgery is to suppress bacterial proliferation, so as to decrease postoperative infection risk. The purpose of this chapter is thus to review the underlying concepts of SSI, allowing us to identify high-risk patients through clinical examination. Correct identification of patients at risk is the starting point of an effective SAP. Identification of high-risk patients establishes a clear basis for SAP prescription. This also allows for the choice of a suitable antibiotic, as well as its proper management through compliance with its method, duration, and frequency of administration. The definition and criteria for classification of SAP have been established by the Centre for Disease Control and Prevention (CDC).¹² It is important to understand how pathogenic agents contaminate the surgical site, how they infect it and how they disseminate in adjacent tissues and organs. It is also important to understand how in some cases, they cause septicemia. A review of these important concepts will help us to better understand what SSI preventive measures are all about, in order to be able to analyze the findings of various studies and trials on the topic.

I-2 Identification of a SSI

Surgical site infection occurs when microorganisms from endogenous or exogenous origin enter the surgical site at different levels: skin or deep tissues. Infection can develop at any time, generally from the first to the 30th day after surgery. Surgical site infection can occur on three levels:

1-Superficial infection: occurring within the first 30 days following a surgical procedure and affecting the skin and sub-aponeurotic tissues;

2-Deep infection: arising within the 30 days following surgical procedure, with this period being prolonged to a year if a prosthetic material is inserted;

3-Infection of an organ or a cavity occurring during the 30 days following a surgical procedure (or a year afterwards if a prosthetic material is used), involving an organ and/or cavity manipulated during the operation.

Therefore, the required antibiotic for SSI prevention must significantly reduce the concentration of micro-organisms during the entire operation on the skin as well as in underlying deeper tissue.

I-3 Rates of surgical site infection

Incidence rates of SSI in the four different classes (clean, clean-contaminated, contaminated and dirty wounds (Table 1) have been published in many studies.

Table 1: les Classification of surgical wounds based on the degree of microbial contamination in postoperative site infections.

CATEGORY OF SURGERY	Infection rate	
	Without antibiotic	With antibiotic
Clean surgery	1 to 5%	<1 %
Clean-contaminated	5 to 15%	<7%
Contaminated surgery	> 15%	<15%
Dirty surgery	>30%	Decrease

(Adapted from: Berard F et al ¹³ and Altemeier W ¹⁴)

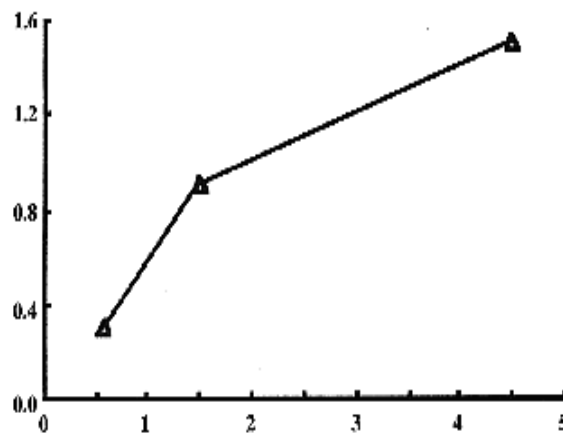
Most literature refers to the work of Cruse et al¹⁵ as a benchmark for infection rates. Before the routine use of prophylactic antibiotics, infection rates were 1-2% for clean wounds, 6-9% for clean-contaminated wounds, 13-20% for contaminated wounds and about 40% for dirty wounds.¹⁵ Since the introduction of routine prophylactic antibiotic use, infection rates in the most contaminated groups have reduced drastically. Infection rates in USA National Nosocomial Infection Surveillance (NNIS) system hospitals are reported now to be as followed: clean: 2.1%,

clean-contaminated: 3.3%, contaminated: 6.4% and dirty: 7.1%.¹⁶. There is, however, considerable variation in each class according to the type of surgery being performed.

I-4 Microbial contamination of the surgical site

I-4-1 Contamination sources

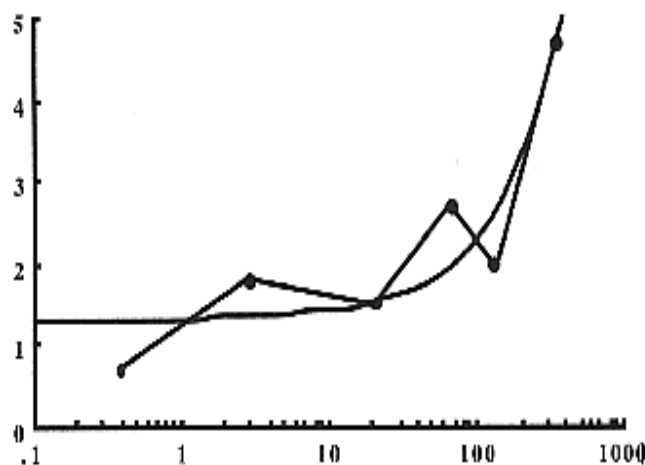
The contamination of a surgical site arises mostly during the preoperative period.^{17,18} It can occur endogenously from the microbial flora present on the patient's skin and mucosal tissues before incision. The contamination can also be exogenous, arising from the skin flora of the staff present in the operating room.¹⁸ Surgical site contamination will inevitably occur in spite of any prior precautions. Martin et al¹⁹ have shown that pathogenic bacteria are present at the moment of surgical wound closure in more than 90% of surgical patients, regardless of surgical hygiene or of prophylaxis which have been used to avoid the surgical site infection. Rate of surgical site infection depend on the concentration of micro organisms present on the surgical wound at the moment of it closure (Figure 1).



X: Amount of germs present in the surgical wound at the moment of closure (m³)
Y: Rate of surgical site infection (%)

Figure 1: Number of microbial agents present in the surgical wound, related with the rate of contamination (Adapted from Lidwell O et al ²⁰)

Lidwell et al ²⁰ have shown that the incidence rate of SSI depends on the amount of microorganisms that are present in the air at the moment of surgery (Figure 2).



X: Concentration of micro-organisms in air (m3)
Y: Rate of surgical site infection (%)

Figure 2 : Relationship between the concentration of infectious particles present in surgical wound and the rate of contamination. (Adapted from: Lidwell et al ²⁰)

This author has shown that the incidence rate of surgical site infection is proportional to the concentration of microbial particles in the surrounding air of the surgical room. These various modes of contamination can co-exist, but their respective roles are variable according to the surgical specialty and the organization of the operating room.

I-4-2 Factors influencing surgical site contamination

Many factors influence surgical wound healing and determine the potential incidence of infection²¹. The level of bacterial concentration is the most important risk factor,^{13,22,23} but modern surgical hygiene techniques and the use of prophylactic antibiotics have reduced this risk. A system of classification for surgical site that is based on the degree of microbial contamination was developed by the US National Research Council group ²¹(Table 2).

Table 2 : Classification of operative wounds based on degree of microbial contamination

Classification	Criteria
Clean	Elective, not emergency, non-traumatic, primarily closed; no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary and genitourinary tracts not entered.
Clean-contaminated	Urgent or emergency case that is otherwise clean; elective opening of respiratory, gastrointestinal, biliary or genitourinary tract with minimal spillage (e.g. appendectomy) not encountering infected urine or bile; minor technique break.
Contaminated	Non-purulent inflammation; gross spillage from gastrointestinal tract; entry into biliary or genitourinary tract in the presence of infected bile or urine; major break in technique; penetrating trauma <4 hours old; chronic open wounds to be grafted or covered.
Dirty	Purulent inflammation (e.g. abscess); preoperative perforation of respiratory, gastrointestinal, biliary or genitourinary tract; penetrating trauma >4 hours old.

(Adapted from Berard et al ²¹)

I-4-3 Microbial proliferation in the surgical site

The starting point of the development of a SSI is the contamination and the colonization of the surgical site by pathogenic agents. It is not necessary that the amount of micro-organisms contaminating the operative site be particularly high in order to cause a SSI. Proliferation of micro-organisms is necessary, and this depends on the environment. Bacteria could find a favourable environment for their proliferation at the surgical site, such as the presence of haematoma, ischemia, and disturbance of the local oxydo-reduction mechanisms. Surgical site contamination does not always lead to SSI. Some factors can favour the evolution of the process towards the site infection.

I-4-4 Factors depending on germs

I-4-4-1-The virulence of a germ

This is the ability of any microorganism to produce disease. The virulence defines the amount of microbes needed to cause an infection. Toxin secretion increases the capacity of microorganisms to survive and invade host tissues, through the rupture of host defense barriers and the alteration of the cellular metabolism.

I-4-4-2-The germ concentration in the surgical site at the time of the contamination.

It has been shown that surgical site contamination with more than 10^5 micro-organisms per gram

of tissue markedly increased the risk of SSI occurrence.¹⁵

I-4-4-3-The pathogenic capacity of the germ.

This results from dissemination of the microorganism starting from the point of entry. We differentiate between two types of pathogenic agents, according to whether bacterial multiplication takes place inside or outside a cellular compartment (intracellular and extra-cellular microorganisms respectively).

I-4-5 Factors related to the patient:

The resistance of the host to infection can be altered by some conditions that are related to patient. Old patients for example are more susceptible to surgical site infection than young one. Patients with pre-existing urinary tract or skin infection are more likely to develop SSI. Chronic diseases like diabetes mellitus and the patient nutritional status also decrease his capacity to resist to microbial infection. Micro-organisms can then proliferate at the operation site.

I-4-6 Factors related to surgery:

Factors related to surgery include duration of procedure. Long surgical procedures are frequently related to SSI. The type of operation and implants are also determinant. It is known that the presence of prosthetic implants in tissue reduces the amount of micro-organisms required to cause surgical site infection.

I-5 Microorganisms most frequently responsible for SSI

I-5-1 Bacteria

Micro-organisms implicated in SSI vary according to the degree of contamination at the surgical site. For operations on the digestive tract, as well as the gynecological or urinary tract, the most frequently germs found are: enterobacteria sp, enterococci sp, streptococci sp and anaerobic bacteria. *Staphylococcus aureus* and coagulase negative staphylococcus are the most frequently germs found in skin surgery.²¹ Andrajati et al.²⁵ have identified *S. aureus* as the most frequent pathogen in surgical site infection. This germ was detected in 90.8% of all cases. A prospective study has found a global SSI incidence rate of 9.6%, with a prevalence of *S. aureus* in 29.1% of cases.²⁶ The pathogens involved are usually those from the visceral flora in the proximity, or

their cutaneous or mucous coverings which have been breached by the incision of the surgeon. Associated bacteria are thus very different, depending on the type of infection. The National Nosocomial Infection Surveillance System of the United States of America has published a list of the most common pathogen agents that has isolated in infected surgical site between **1986** to **1996** (Table 3).

Table 3 : Distribution of Pathogens Isolated From Surgical Site Infections (NNISS 1986 to 1996)

Pathogens	Percentage of isolates	
	1986-1989 ³² (N=16,727)	1990-1996 ³¹ (N=17,671)
<i>Staphylococcus aureus</i>	17	20
Coagulase-negative staphylococci	12	14
<i>Enterococcus sp.</i>	13	12
<i>Escherichia coli</i>	10	8
<i>Pseudomonas aeruginosa</i>	8	8
<i>Enterobacter sp.</i>	8	7
<i>Proteus mirabilis</i>	4	3
<i>Klebsiella pneumoniae</i>	3	3
Other <i>Streptococcus sp.</i>	3	3
<i>Candida albicans</i>	2	3

(Adapted from Mangram A et al ²⁴)

I-5-2 Antimicrobial-resistant pathogens

Surgical literature reports a constant increase in the rate of SSI caused by antimicrobial-resistant pathogens. The most frequent pathogen found in this category of infections is the methicillin-resistant *S. aureus* (MRSA).²⁷

I-5-3 Fungi

Fungal involvement in SSI is also on the rise. Patients who have benefited from abdominal surgery are known to be particularly at risk for candida infections. In a multicenter study done for the NNIS by Jarvis et al, *Candida albicans* was reported by this author as an increasing etiology of SSI.²⁸ Additionally, Mc Neil et al ²⁹ found that *Candida albicans* was the cause of 1% (4 out of 364) fungemia-associated SSI registered SSI in their hospital in one month.

I-6 Risk factors for SSI

Risk factors for SSI can be divided in two principal categories (table 4): patient-related factors and surgery-related ones.

Table 4 : Risk factors for surgical site infection

Risk factors for Surgical Site Infection in Order of Importance	
Risk factors	Current recommendation
Patients related	
Diabetes mellitus	Strict perioperative glycemic control (< 200mg/dl)
Urinary tract infection	Postpone elective surgeries for chronic incorrectable urinary tract infection in the presence of diabetes mellitus. consider lifelong antibiotics
Chronic renal failure	Preoperative haemodialysis
Rheumatoid disease	For alteration in steroidogenesis because of systemic use of steroids, consider drug changes
Immunocompromise	Monitor for opportunistic infections and other risk factors for surgical site infection
Obesity	Minimized wound trauma during exposure
Nutritional status	Consider preoperative supplementation
Smoking	Consider cessation even after surgery
Chronic conditions (eg: Hypertension, chronic obstructive pulmonary diseases, etc...)	For impaired oxygen saturation in surgical side , reduce tourniquet , surgical time, bleeding
Surgery related	
Blood transfusion	Autotransfusion preferred; minimize intraoperative and postoperative bleeding by regional hypotensive anaesthesia, revising medication and good preoperative planning
Hypothermia	Avoid
Surgical technique	Minimized soft-tissue trauma and vascular disruption , especially around wound edges
Preoperative skin préparation	
Intraoperative issues (eg :Laminar flow, operating room routines)	
Postoperative issues	Effective and timely use of prophylactic antibiotics ,decrease hospital stays

(Adapted from Gurkan I et al ³⁰)

It is necessary to assess these risk factors in each patient in order to boost the effectiveness of SAP. This prior assessment assists the surgeon in making appropriate decisions about the indication of SAP. It is clearly established that in some operations, the individual risk factors in a particular patient can be responsible for an increased possibility of infection. These factors include coincident remote site infections ^{31,32} germ colonization ^{33, 34} diabetes ^{35, 36} cigarette

smoking,^{37- 39} systemic steroid use,² obesity (superior to 20% of the ideal body weight),⁴⁰ extremes of age,⁴¹ poor nutritional status,⁴² and perioperative transfusion of blood products.⁴³

I-7 Summary

Appropriate SAP practice requires good knowledge of the pathological mechanisms of SSI, the associated bacteriological mechanisms, the integration of unusual agents like fungi, the epidemiologic characteristics, and the risk factors. A correct SAP practice depends largely on a strict application of the fundamental principles which are now well established and whose importance has been sufficiently shown. A careful assessment of the patient's risk factor is not to be neglected.

Part II

Assessment of appropriateness of antibiotic prophylaxis principles in common surgical procedures

II-1 Material and Methods

This chapter will review, summarize and discuss the main findings of different studies about the appropriateness of antibiotic prophylaxis practice in patients receiving surgical treatment. The goal is to investigate the very high incidence rate of SSI, despite an extended SAP practice. Appropriate SAP practice is considered as a practice that conforms to the recommendations of guidelines. Inappropriate SAP practice is thus a practice that is not concordant to such recommendations.

III-1-1 Literature search strategy

Studies assessing SAP principles were identified using the Cochrane library. The following keywords were used: “surgical antimicrobial prophylaxis”; “compliance with antibiotic prophylaxis in surgery”; “antimicrobial prophylaxis, audit recommendations”; “surgical antibiotic prophylaxis evaluation”. Relevant studies were collected.^{2, 5, 40, 44 - 70}

III-1-2 Inclusion criteria

Prospective clinical studies assessing the appropriateness of the SAP practice in patients Undergoing various surgical procedures were included. The selected studies had to evaluate one or several of these five main SAP principles: 1-the indication of SAP, 2-the antibiotic chosen, 3-the dose of the antibiotic used for SAP, 4-the timing of the first administration of the chosen antibiotic, 5-the duration of the antibiotic administration.

III-1-3 Exclusion criteria

Retrospective studies and studies based on questionnaires to be filled in by surgeons, anaesthetists or nurses were excluded. Review and meta-analysis studies were also excluded.

III-1-4 Data extraction

In this review, the rate of inadequate practice of SAP principles is used as the principal outcome measure to assess the quality of SAP practice. Among the infection prevention measures, only SAP was considered, owing to its reliability. Other preventive measures such as surgical hygiene techniques were not considered.

III-1-5 Data synthesis

The outcome: ‘‘Inadequate rate’’ (R) was collected in each study. This was subdivided into: The rate of inappropriate SAP indication (R_1); The rate of inappropriate antibiotic selection (R_2) ; The rate of Inappropriate antibiotic dose (R_3) ; The rate of inappropriate antibiotic timing of administration (R_4) ; The rate of inappropriate SAP duration (R_5). The rate of global inappropriate SAP practice (R_6). The collected data from each evaluated SAP principle were grouped together

III-1-6 Statistical analysis

Data were analyzed using Microsoft Excel 2003. In order to be able to perform a reliable quantitative assessment of the outcome, the implementation of each SAP principle was considered as inappropriate in the case when $R > 20\%$.

II-2 Results

Thirty studies met the selection criteria, involving a total of 28'822 patients. All the included studies assessed the appropriateness of SAP practice and were published between 1993 and 2007. Table 5 summarizes the characteristics of the studies included in this review.

Table 5 : Rates of inappropriate implementation of each of the five SAP principles reported in the included studies

Study	Year	Country	Overall A	Indication B	Dose C	Timing D	Duration E	Antibiotic F
Dellamonica ²	2002	France			3%	11%	20%	13%
Khan ⁵	2006	India				0%	92.80%	
Bratzler ⁴⁰	2005	USA				44.30%	59.30%	8%
Queiroz ⁴⁴	2005	Brazil		15.20%	63.7%	20%		1.70%
D'Esquivan ⁴⁵	2004	France	50.00%	49 %				
Talon ⁴⁶	2004	France	77.60%	29.10%	35.7 %	42.90%	15.70%	80%
Da Col ⁴⁷	1993	France	41.50%					
Kalle ⁴⁸	2005	Tunisia	46.10%	3.10%			30,5 %	37,6 %
Noleen ⁴⁹	2006	Austria				47.30%	23.90%	47.40%
Tourmousoglou ⁵⁰	2007	Greece	63.70%	19%		0%	63.70%	30%
Van Kasteren ⁵¹	2005	Netherlands	93.50%			51.8%	46.80%	
Gilles ⁵²	2002	France	42.00%	10%	8%	4%	20%	10%
Bull ⁵³	2005	Austria	18.90%	65%		23.60%		23.90%
Bussi�res ⁵⁴	2004	Canada	69.00%		25.%			
Hing ⁵⁵	2005	Singapore	87.20%		26.3%		54.40%	42.70%
Rioux ⁵⁶	2002	France	66.00%			30%	22%	
Daurat ⁵⁷	2000	France	20.00%	18%	11%	40%	15%	20%
Gomez ⁵⁸	2006	Argentina	26.00%				56%	
Won ⁵⁹	2007	Korea			21.1%	88.80%	99.80%	
Van Kasteren ⁶⁰	2003	Netherlands	72.00%		11%	50%	18%	8%
Van Disseldorp ⁶¹	2006	Nicaragua	93.00%	23%	20%		78%	69%
Yalcin ⁶²	2007	Turkish				100%	71%	
Nunes ⁶³	2006	Brazil	1.00%		1%	7%		
Wybo I. ⁶⁴	2004	Czech	27.00%	95.20%				
Bedouch ⁶⁵	2004	France	47.00%		2%	20%	2%	29%
Zanotto ⁶⁶	2006	Brazil			0%	18.20%	19.50%	5%
Vaisbrud ⁶⁷	1999	USA	33%			0%	4%	5%
Bailly ⁶⁸	2001	France	58.3%				17 .7%	22.8 %
Chen ⁶⁹	2002	Taiwan				23.8%		
Sae-tia ⁷⁰	2006	Thailand	24.8%					

A: Overall rate of inappropriate SAP practice in each study

C: Rate of inappropriate drug dose administrated for SAP in each study

E: Rate of inappropriate duration of drug administration during SAP in each study

NB: The five principles was not assessed in all the studies

B: Rate of inappropriate indication of SAP in each study

D: Rate of inappropriate timing of administration of the first dose of drug for SAP in each study

F: Rate of inappropriate antibiotic choose for SAP in each study

Regarding the origin of the studies, there were mainly from: France (26,7%) and Brazil (13,3 %). In table 6 the number of studies included in this review are listed per country.

Table 6 : Number of included studies per country

Country	Number of study included	Percentage
France	8	26.7
Brazil	4	13.3
Austria	2	6.7
Netherlands	2	6.7
USA	2	6.7
Tunisia	1	3.3
Greece	1	3.3
Canada	1	3.3
India	1	3.3
Singapore	1	3.3
Argentina	1	3.3
Korea	1	3.3
Nicaragua	1	3.3
Turkish	1	3.3
Czech	1	3.3
Taiwan	1	3.3
Thailand	1	3.3
Total	30	100

None of the thirty studies reported the data for all five SAP principles. The rate of inappropriate SAP indication was recorded in 10 of the 30 studies. The indication of SAP was inappropriate in 8 studies (80%). The Figure 3 illustrates the statistical features of inappropriate SAP indication.

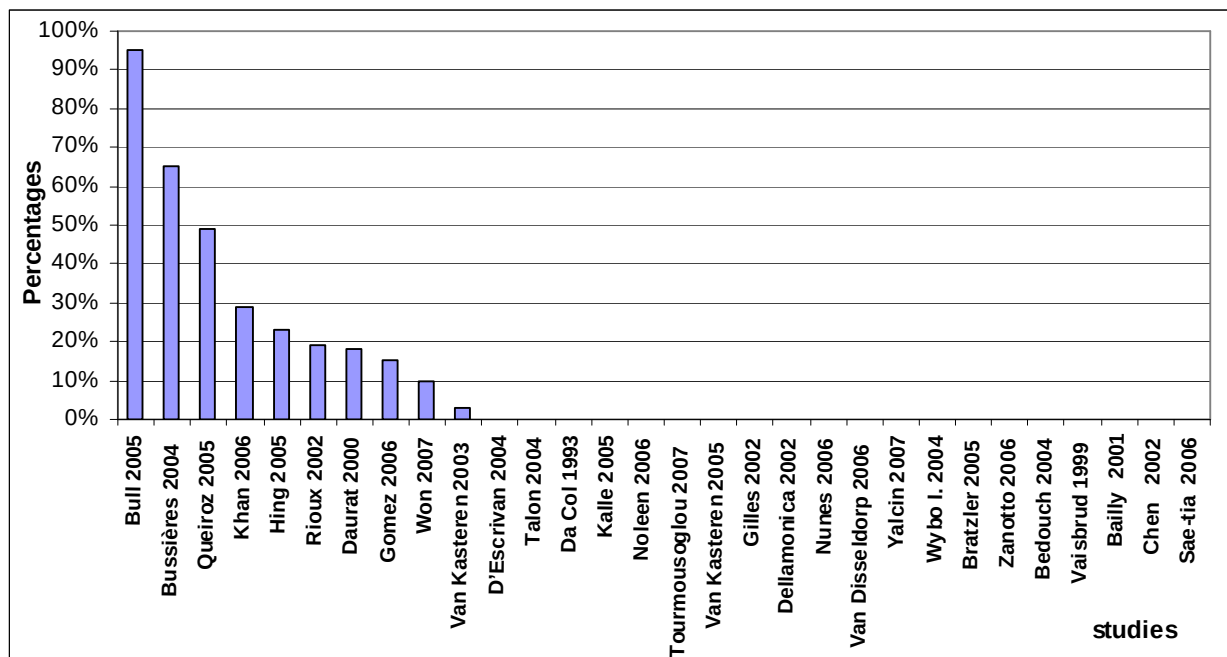


Figure 3 : Diagram representing the proportions of inadequacies in SAP indication for each study.

The overall appropriateness of SAP practice was assessed in 20 of the 30 studies. The overall SAP practice was inappropriate in 18 studies (90 %).

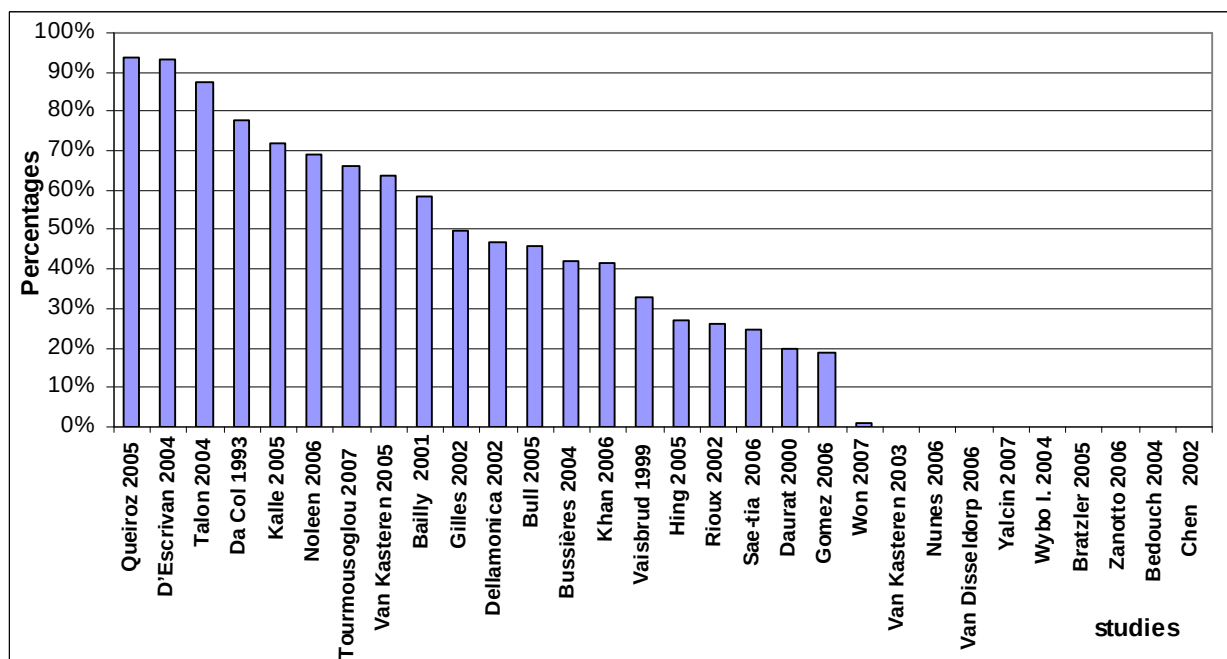


Figure 4 : Diagram representing proportions of global inadequacies of SAP principles in each study.

Appropriateness of the antibiotic selection was assessed in 17 of the 30 studies. The antibiotic

chose was inappropriate in 9 studies (52.9 %). The figure 5 illustrates the statistical features of inappropriate antibiotic selection.

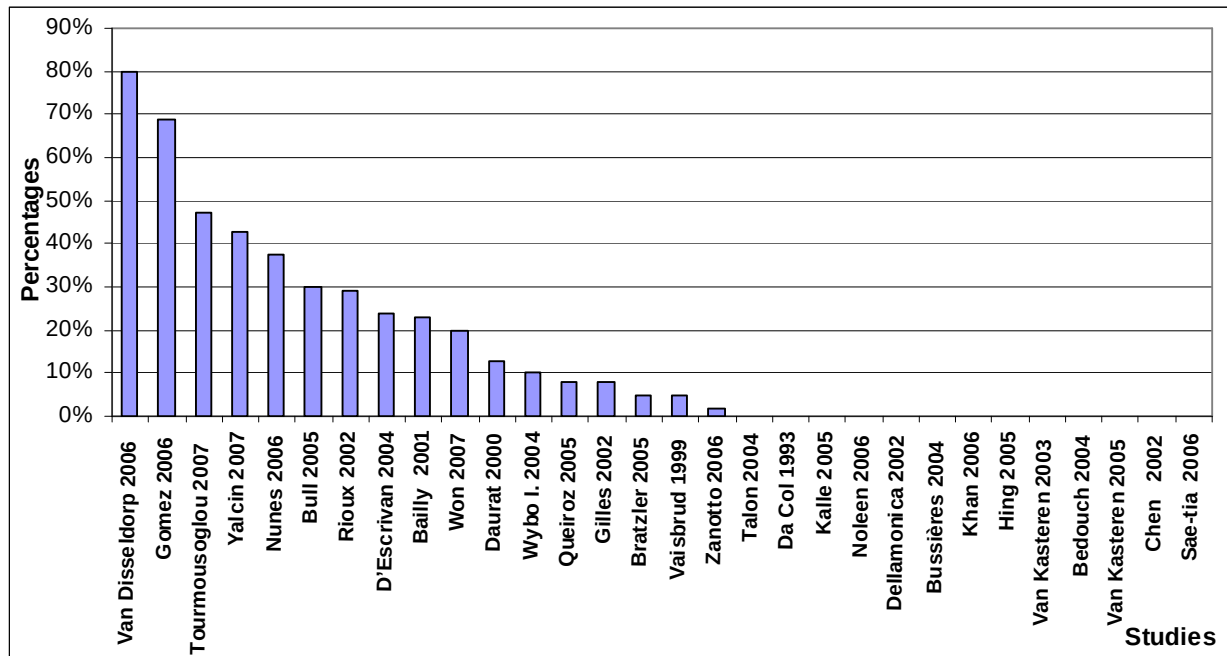


Figure 5 : Diagram representing the profile of mistakes in antibiotic selection in each study

The rate of inappropriate dose of antibiotic for SAP was recorded in 13 of the 30 studies. The dose of antibiotic for SAP was inappropriate in 5 studies (38.4%).

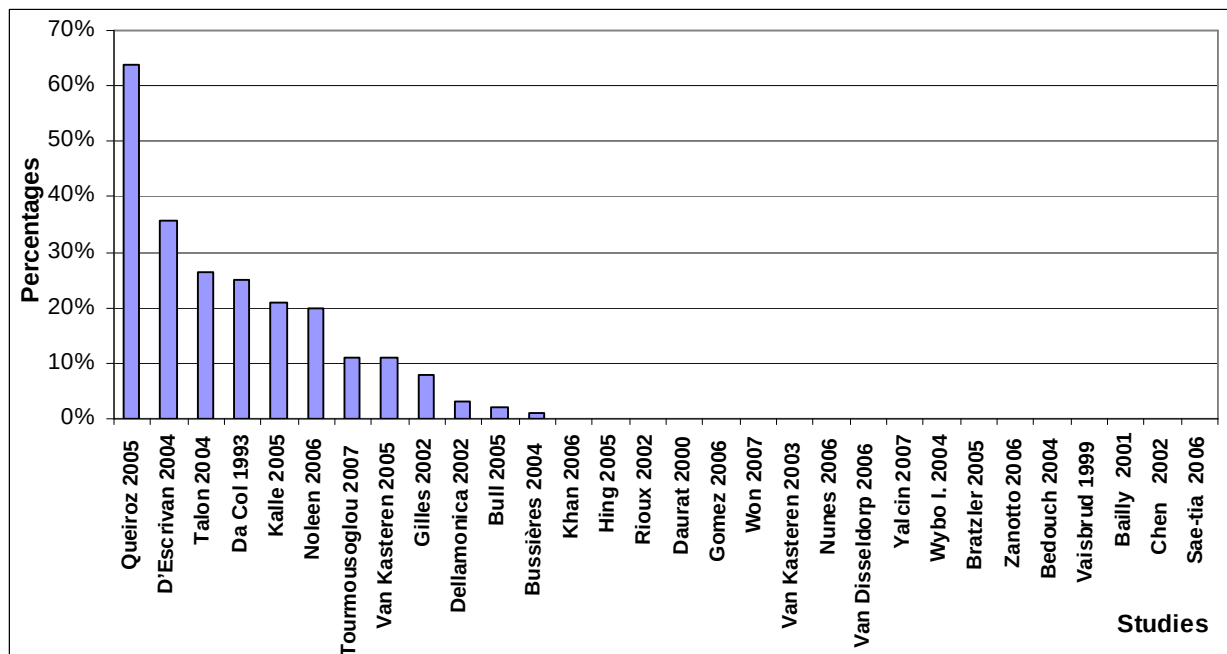


Figure 6 : Diagram representing the inadequacies of dose of antibiotic in each study

The rate of inappropriate timing of antibiotic administration was recorded in 20 of the 30 studies.

The timing of the antibiotic administration for SAP was inappropriate in 5 studies (25 %). Figure 7 gives an illustration of the inappropriate timing of antibiotic administration.

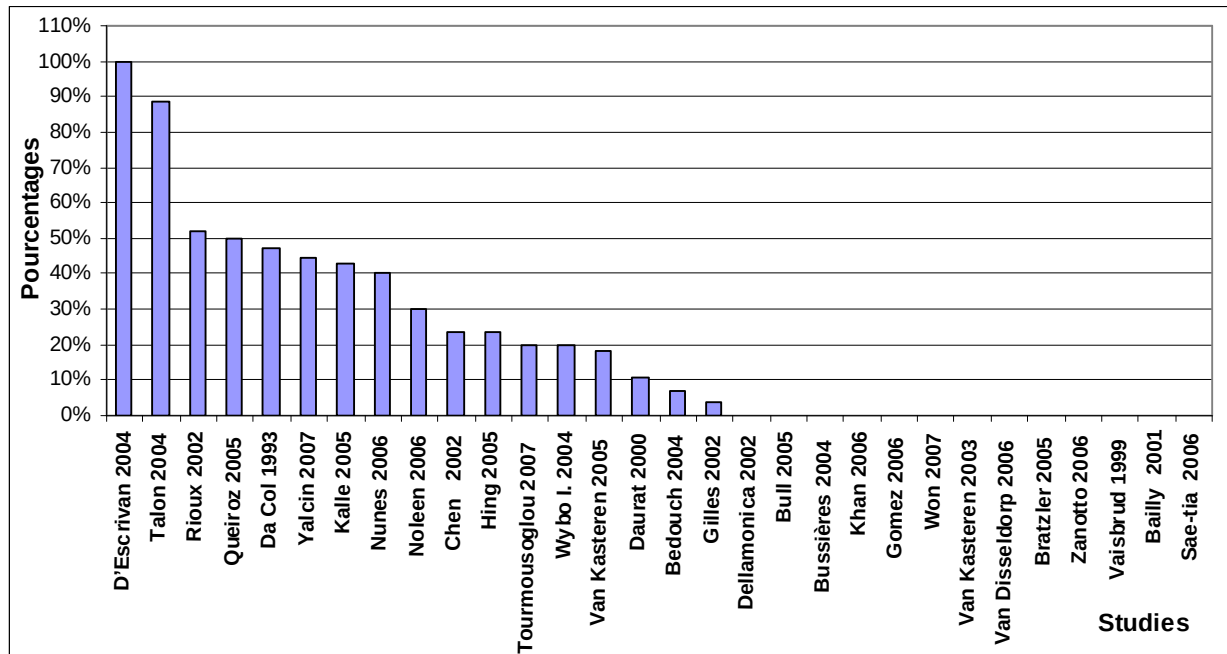


Figure 7 : Proportion of error in timing in each study

Duration of antibiotic administration was assessed in 21 studies. The duration of AB administration was inappropriate in 12 studies (57.1%)

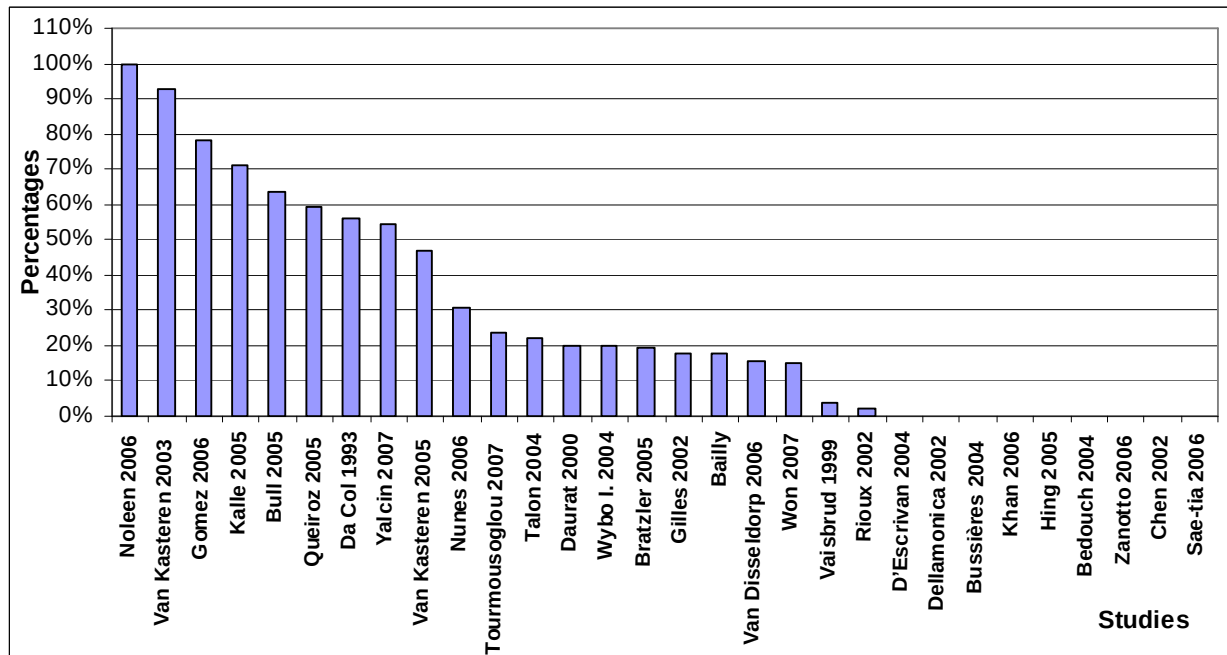


Figure 8 : Diagram representing the profile of inappropriate SAP duration in each study.

Duration and timing of antibiotic administration (Figure 9) were the two most inappropriate components found in terms of importance and frequency.

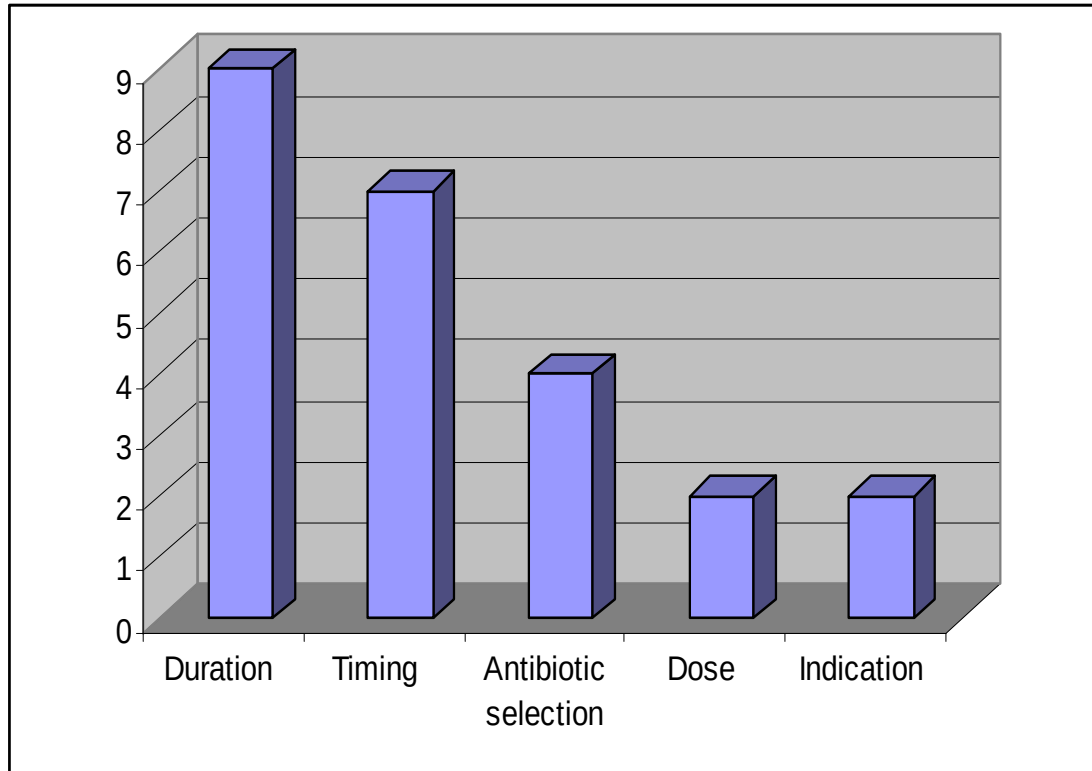


Figure 9 : Rates of inadequacy of the five SAP regimen components

II-3 Discussion

II-3-1 SAP Indication

SSI tends to be considered as one of the complications to be absolutely avoided in modern surgery practice. Indeed, it is becoming more and more difficult to justify this post-surgical complication. Patients demand more and more accountability for the results the operation. They seem to be particularly attentive to the intervention outcome, particularly infectious complications. Thus, the decision to administer SAP is often based on fear of legal repercussions rather than on scientific evidence of actual patient benefit, even when such measures are not necessary. Besides this, most surgical teams tend to practice an empirical and systematic surgical antimicrobial prophylaxis, without paying attention to whether it is necessary. Analysis of results of the various audits on the SAP practice carried out in many parts of the world shows that indication of SAP is not always clearly shown.⁷¹⁻⁷³ The outcome of these audits reveals that the

decision to put patients under SAP seems to be taken at random, without objective scientific criteria. This seems to be a general tendency in current surgical practice. A recent multi-center study conducted in Belgium in 58 acute care hospitals, including 19'746 patients, showed that SAP was given in 57% of surgical patient without clear indication⁷⁴. Dellaminica² attributes this tendency to prescribe systematic SAP to hyper-sensitization about SSI and their consequences. However, as we stated in Part I of this thesis, this attitude is dangerous: indeed, inappropriate antibioprophylaxis increases selection pressure and favours emergence of resistant micro-organisms. Even if surgical antibioprophylaxis is appropriately used, it can induce modifications in endogenous bacterial flora of the digestive tract, as well as the skin and the mucous tissues. This can result in germs' resistance to the particular antibiotics that have been used. This was shown by Archer et al⁷⁴; by Fukatsu et al;⁷⁵ by Kermode et al.⁷⁶ and by Maki et al.⁷⁷

II-3-2 Antibiotic selection

Appropriate antibiotic selection in SAP always takes into consideration the bacterial ecology specific to the milieu and the type of surgery to be performed. International guidelines have published lists of pathogenic agents that are commonly responsible for SSI in each type of surgery, as well as appropriate antibiotics. A comprehensive risk assessment should be a part of the process of choosing the appropriate antibiotic.⁷⁸ This should include possible adverse effects.⁷⁹⁻⁸¹ It was found that inappropriate antimicrobial selection represents the third most important mistake in SAP inadequacies. In general, surgical teams are not sufficiently compliant with established consensus on the choice of antibiotic. Gilles et al carried out a series of two audits on the practice of SAP.⁵² The authors noticed discordances between local recommendations and clinical practice. In their first assessment, they found that the rates of inappropriate choice of antimicrobial agent were very high, (42%). Subsequently, they proceeded to a corrective intervention in order to improve this situation. They carried out a second assessment and noted that the rate of inappropriate choice of antibiotic had increased to 50 %. This shows surgeons' resistance to implementing the recommendations of guidelines. For Gilles et al,⁵² this discordance is mostly due to excessive precautions: surgeons who were involved in his study have prescribed unjustified and useless combinations of several antimicrobial agents. In the same way, other studies on SAP principles evaluation carried out in Europe and America show that the antimicrobial agents chosen for SAP are inappropriate. Some features concerning this

inappropriate choice are recalled here: 25% in the study of Dellamonica ²; 18% in the study of Daurat et al, ⁵⁷ and 53,9% in the study of Kalle et al. ⁴⁸ In some cases, efficient interventions have been reported. Desrivain et al, ⁴⁵ in their study after a corrective intervention and follow-up, noted a clear improvement in the choices of antimicrobial agents used for SAP. They reported that this improvement was due to the pharmacy. The hospital's pharmacy had spontaneously proceeded to restrict the quantity of antibiotics available for SAP. The pharmacy's intervention was not planned in the protocol of their study. They thus fortuitously noted the positive role which restrictive measures can play in the optimization of the surgical antimicrobial prophylaxis. This important positive role of pharmacy intervention has also been reported in Belgium ⁸² Broad-spectrum antimicrobial agents increase healthcare costs without any obvious advantage in SSI prevention.

II-3-3 Dose

Dose selection of antibiotic represents the fourth most important source of mistakes in SAP practice. ¹⁰⁶ Several studies have shown that it is benefic to administer additional doses of antibiotic during the intervention in long-lasting surgery (more than three hours). ^{40,107,108} The need to administer additional doses of a prophylactic antimicrobial agent in a surgical procedure of short duration has not been clearly defined. Many studies comparing preoperative single doses to multiple doses in SAP have not shown the benefit of additional doses. ^{83- 88} For Pea et al, ⁸⁹ a lack of clear distinction between antimicrobial prophylaxis and therapy exists in surgery. It is believed that to maintain optimal serum concentrations of antimicrobial agents in a very long perioperative surgical period (as done in therapy) is more effective in SSI prevention. This has justified the practice adopted by many surgeons of administering several antimicrobial doses in short-duration surgery. ⁹⁰ Such attitudes can be justified in therapy, but do not make sense in SAP. This is because in prophylaxis, the antimicrobial molecule only has to be present on the surgical site at the moment of the possible contamination in order to prevent and maintain microbial concentration under the infection threshold throughout the whole surgical procedure. Thus, SAP is first of all a procedure which aim is to reduce the amount of bacteria at the surgical site, to avoid infection. This is why a single dose of antibiotic is sufficient in short-duration surgery. ^{91,92} In the case of long duration surgery, it may be necessarily to administrate additional dose of antibiotic. Administration of inappropriate doses can be considered as the result of

ignorance and unwillingness: studies have shown that when protocols regarding drugs and doses are provided, the situation improves.⁹³ For this reason, some researchers have successfully used pre-established evidence on which to base protocols with drug and doses included.^{94, 95; 96} In the same way, Queiroz et al⁴⁴ have reported a significant improvement in dose prescription of antimicrobial use for SAP. This dose prescription improvement was more significant than other variables after he had introduced a SAP protocol in their institution.

II-3-4 Timing

There is a close relationship between the timing of administration of the first dose of antibiotic and the effectiveness of SAP. These two important factors are described as essential for SSI prevention.^{97, 98} For Woods et al,⁹⁹ the timing of antibiotic administration is critical in surgical site infection prevention practice. The antimicrobial prophylaxis must be administered a few minutes before the beginning of surgery, generally at the time of anaesthetic induction.^{100 - 103} In order to prevent subsequent infection, the antibiotic must be present in the patient's tissues at the time of bacterial contamination. Studies have shown that administration of prophylactic antimicrobial drugs within a period of two hours before surgery significantly reduces the risk of wound infection. A common habit among surgeons is to administer antibiotic not before but, after the surgical procedure¹¹⁰, in spite of strong data which proves that this practice is not benefic. This review obviously shows that timing is the second most important mistake in SAP practice. It can be argued that inappropriate timing plays a great role in decreasing the effectiveness of SAP. Wendy et al¹⁰⁹ found the same result. Alerany et al¹¹⁰ have reported that timing of antimicrobial administration was the main cause of antimicrobial prophylaxis misuse. In Tourmousoglou et al's study,⁵⁰ 100% of patients overall received perfectly-timed antimicrobial prophylaxis. The author attributes this result to the routine of initiation of prophylaxis by anesthesiologists at the time of induction of anesthesia. In accordance with this report.

II-3-5 Duration

Inappropriate SAP duration was the most frequent and important mistake in this review. Tourmousoglou et al.⁵⁰ have also reported a major misconception among surgeons regarding the need for prolonged administration of antimicrobial prophylaxis. Generally, the duration of prophylaxis should be short, and should not be extended beyond the minimum period known to

be effective. According to a consensus, the duration of SAP should be less than 48 hours.⁴⁹ However, studies have shown that prolonged antibiotic treatment after wound closure has no benefit in surgical site infection prevention.^{104,111-116} Excessive duration of antibiotic prophylaxis is one of the most common errors in surgical antibiotic prophylaxis,¹¹⁷ but this error can be corrected by sensitization. In D'Escrivan's study⁴⁵, only the global conformity rate in relation to the duration of SAP improved significantly after a three-month sensitization period.

Part III

Review of randomized control trials on SAP, comparatively to placebo therapy in the reduction of incidence of post surgical infectious complications

III-1 Material and Methods

This chapter will review, summarize and discuss the main findings of randomized control trials, to assess the efficacy of antimicrobial prophylaxis in patients receiving surgical treatment. The goal is to analyze results of the trials and assess their value, in relation to the various methodologies used by authors. An effort will be made to investigate the paradoxical and contradictory results in the medical literature about the incidence rate of SSI, in light of the expected findings.

III-1-1 Definition of statistic methods used in this analysis:

III-1-1-1-The Mantel-Haenszel model

This is a statistical method that has been designed to test the association between two dichotomous variables using information from several 2x2 tables. This statistic is extended here for incidence data on a rare outcome arising at two or more levels of an exposure variable.

III-1-1-2-The funnel plots

A funnel plot is a scatter-plot of treatment effect against a measure of study size. It is used primarily as a visual aid to detecting bias or systematic heterogeneity. A symmetrically inverted funnel shape arises from a 'well-behaved' data set, in which publication bias is unlikely. An asymmetric funnel indicates a relationship between treatment effect and study size. This suggests the possibility of either publication bias or a systematic difference between smaller and larger studies ('small study effects'). Asymmetry can also arise from use of an inappropriate effect measure. Whatever the cause, an asymmetric funnel plot leads to doubts over the appropriateness of a simple meta-analysis and suggests that there needs to be investigation of possible causes.

III-1-2 Literature search strategy

All randomized controlled trials comparing preoperative antibiotics versus placebo were searched using the Cochrane Library data base. The following mesh terms were used: "Antimicrobial prophylaxis in surgery"; "Antibiotic use in surgery"; "surgical site infection prevention"; "surgical wound infection"; "infection complication in surgery".

III-1-3 Inclusion criteria

This intervention review includes prospective randomized controlled trials, (Antibiotics versus placebo) that evaluate antimicrobial prophylaxis in the prevention of surgical site infection in patients who have undergone common surgical procedures. Only antibiotic versus placebo trials was considered for this review. Only trials that presented two branches of experimental groups (one for antibiotic and one for placebo) were included.

III-1-4 Statistical analysis

Data were analyzed using Microsoft Excel 2003 and Revman 5.0 software. The Mantel-Haenszel method with fixed effect in dichotomous data type and chi-square test was used to measure the risk ratio. $P < 0.05$ was considered as statistically significant. The Cochrane test was used to test the heterogeneity of each group. In the case of heterogeneity ($P < 0.05$) with the Cochrane test, the data of the concerning group was considered as uninterpretable. The global effect was estimated, using the Wald test. The funnel plot was interpreted to detect possible publication bias.

III-2 RESULTS

III-2-1 General results

A total of 914 published studies were collected. Among them, 129 pertinent randomized control trials were identified. Seventy-eight trials were then subtracted for incomplete data. 51 trials met the inclusion criteria at this stage. The 51 selected trials were then grouped according to surgical type. Ten single trials could not be included in a group of more than one trial. The 41 trials which were finally selected were then grouped into 7 surgical types (Table 8-14), and involved a total of 8'280 patients. The trials were published between 1978 and 2007. The 41 selected trials were conducted in double or simple blind manner. The languages of publications were English and French. The studies were conducted in 20 different countries, mainly in the United States of America (26.8%), the Netherlands (12.2%) and the United Kingdom (9.8%) table 7 gives the number of included trials per country.

Table 7 : Breakdown of trials per country

Countries	Number of studies	Percentages
USA	11	26.8
Netherlands	5	12.2
UK	4	9.8
Spain	3	7.3
Greece	2	4.9
Turkey	2	4.9
France	1	2.4
Germany	1	2.4
Sweden	1	2.4
Mexico	1	2.4
Philippines	1	2.4
Venezuela	1	2.4
South Africa	1	2.4
Canada	1	2.4
Chile	1	2.4
Brazil	1	2.4
Israel	1	2.4
Poland	1	2.4
United Arab Emirates	1	2.4
Finland	1	2.4
Total	41	100.0

Seven types of surgery were found: tension free-mesh inguinal hernia repair; endodontic surgery; caesarean section; percutaneous endoscopic gastrostomy; hysterectomy; transurethral resection of the prostate and orthopedic surgery. The major outcome: “surgical site infection” was described in all included trials. Table 8 shows the number of trials included for each type of surgery.

Table 8 : Synthesis of the different types of surgical procedures.

Type of surgery	Number	%
Tension free-mesh hernia repair	9	22.0
Endodontic surgery	8	19.5
Cesarean section	7	17.1
Percutaneous endoscopic gastrostomy	6	14.6
Hysterectomy	5	12.2
Transurethral resection of the prostate	4	9.8
Orthopedic surgery	2	4.9
Total	41	100%

III-2-2 Tension free-mesh inguinal hernia repair

A significant heterogeneity ($P=0.04$) was found in 9 trials on tension free-mesh inguinal hernia repair (Table 9, and Figure 10).

Table 9 : Recapitulation of comparative trials in tension free-mesh inguinal hernia repair procedures and main results

Trial	Year	Regimen	Antibiotic Group			Placebo Group		
			N	SSI	%	N	SSI	%
Tzovaras ¹¹⁸	2007	Amoxy /clav	193	5	2,5%	193	9	4,6%
Yerdel ¹¹⁹	2001	Amp.Sulb	140	1	0.70%	140	12	8.5%
Lazorthes ¹²⁰	1993	Cefamandole	162	0	0%	162	7	4.3%
Taylor ¹²¹	1997	Amoxy/clav	283	50	17.6%	280	50	17.8%
Aufenacker ¹²²	2004	Cephalosporin	503	8	1,5%	505	9	1,7%
Celdrán ¹²³	2004	Cefazolin	50	0	0%	49	4	8,1%
Vásquez ¹²⁴	2005	Cephalothin	68	2	2,9%	92	2	2,1%
Perez ¹²⁵	2005	Cefazolin	180	3	1,6%	180	6	3,3%
Camacho ¹²⁶	2005	Ampicillin/Sulbactam	112	0	0%	82	4	4,9%

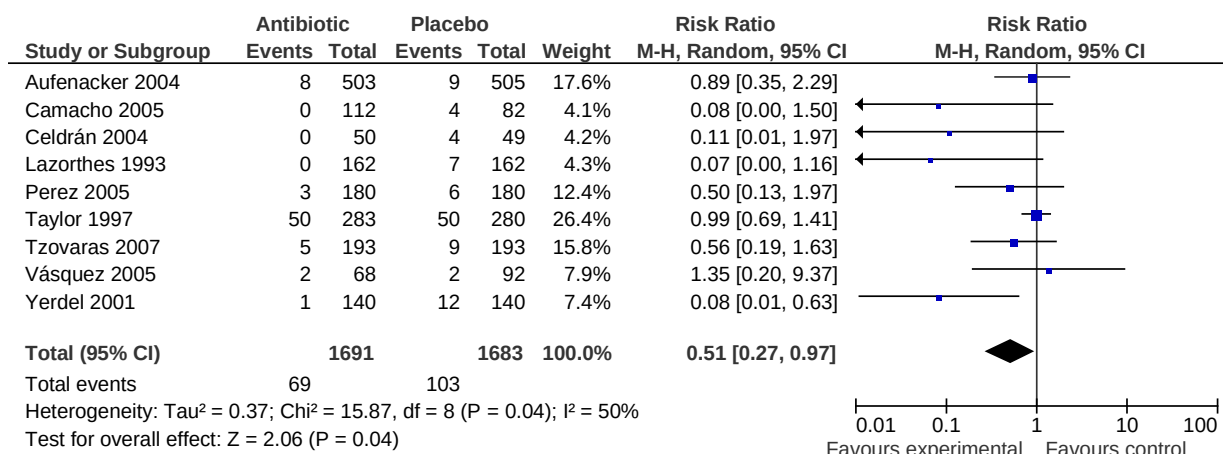


Figure 10 : Antibiotic versus placebo comparison, in tension free-mesh hernia repair

The difference between the two groups was statistically significant ($p=0.04$). Cephalosporin of third generation was the most frequently used antibiotics (55,6%). Six studies out of 9 (66.7%) concluded that there is no statistically significant benefit of antibiotics compared to placebos in SSI prevention.^{118, 121, 122, 124-126} Consequently, the six authors did not recommend systematic SAP in tension free-mesh hernia repair. The funnel plot (Figure 11) is asymmetrical. This confirms the heterogeneity of the two groups. Indeed, the funnel describes a systematic difference between smaller and larger trials in this group of tension free-mesh inguinal hernia repair. A publication bias is suspected.

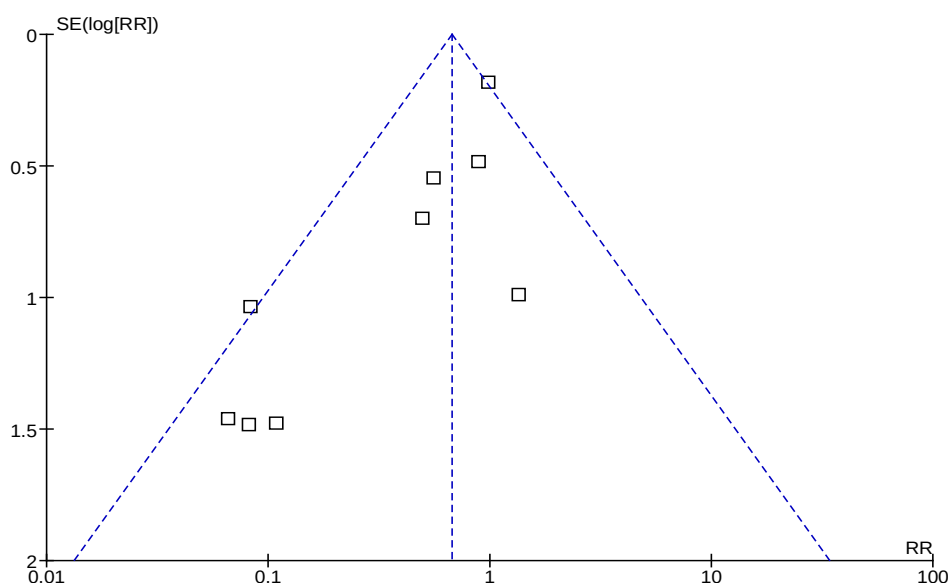


Figure 11 : Funnel Plot effect for tension free-mesh hernia repair

III-2-3 Endodontic Surgery

A significant heterogeneity ($P=0.002$) was found in 8 trials on endodontic surgery. Table 10 and Figure 12 illustrate the statistical features of this group. Owing to the significant heterogeneity of this group.

Table 10 : Recapitulation of comparative trials in third molar surgery

Trial	Year	Regimen	Antibiotic Group			Placebo Group		
			N	SSI	%	N	SSI	%
Lindebomm ¹²⁷	2003	Clindamycin	62	0	0%	62	3	4.8%
Lindebomm ¹²⁸	2005	Clindamycin	128	2	1,5%	128	6	4,6%
Arteagoitia ¹²⁹	2005	Amoxy/clav	259	5	1,9%	231	30	12,9%
Bergdahl ¹³⁰	2004	Metronidazole	59	10	16,9 %	60	12	20%
Lacasa ¹³¹	2003	Amoxy/clav	75	12	16%	75	4	5,3%
Lacasa ¹³²	2007	Amoxy/clav	150	11	7.3%	75	12	16%
Lindeboom ¹³³	2003	Pheneticillin	10	0	0%	10	5	50%
Halpern ⁸¹	2007	Penicillin	59	0	0%	59	5	8.4%

The difference between the two groups was significant ($P=0.04$): Relative risk was 0.42 with a 95% confident interval (0.18, 0.97) (Figure 12).

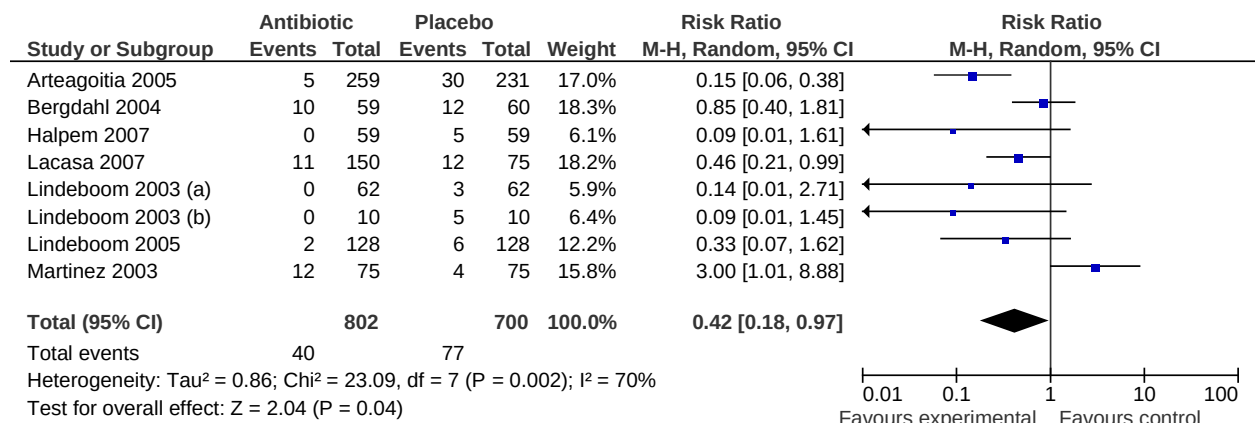


Figure 12 : Antibiotic versus placebo comparison, in endodontic surgery

Amoxicillin combined with clavulanic acid was the most frequently used antibiotic (37,5%). Five authors out of 8 (71.4%) could conclude that there is a benefit of antibiotics compared to placebos in preventing SSI.^{81,127-129,132} In Figure 13, the funnel plot shows an asymmetrical

distribution of trials. This characteristic confirms the heterogeneity of the two experimental groups: the small sample size is in favour of the antibiotic (even the risk ratio was not significantly different from 1). A publication bias is thus suspected.

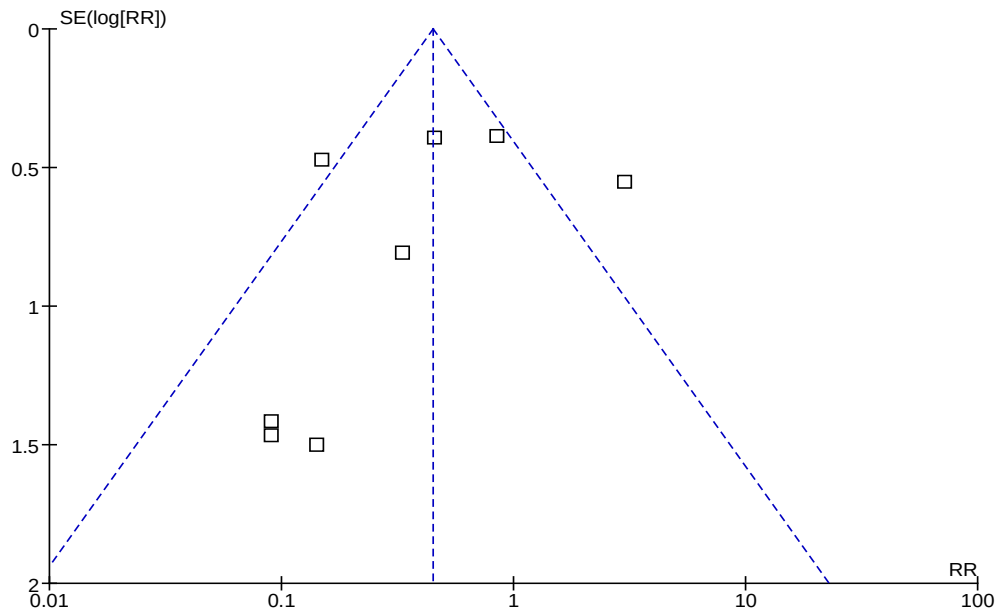


Figure 13 : Funnel Plot effect for endodontic surgery

III-2-4 Caesarean section

No heterogeneity ($P=0.37$) was found in the 7 trials concerning caesarean sections (Table 11 and figure 14).

Table 11 : Recapitulation of comparative trials in Caesarean sections and main results

Trial	Year	Regimen	Antibiotic Group			Placebo Group		
			N	SSI	%	N	SSI	%
Zabramski ¹³⁴	1982	Ticarcillin	139	44	2.8%	120	66	55%
Gall ¹³⁵	1979	Cefazolin	46	8	17.3%	49	19	38.7%
Bagratee ¹³⁶	2000	Cefoxitin	240	20	8.3%	240	19	7.9%
Kreutner ¹³⁷	1978	Cefazolin	13	0	0%	17	2	11.7%
Krasnodebski ¹³⁸	1997	Amoxy/clav	32	0	0%	31	4	12.9%
Rizk ¹³⁹	1998	Cefuroxime	59	2	3.3%	61	3	4.9%
Pitt C ¹⁴⁰	2001	Metronidazole	112	8	7%	112	19	17%

The difference between the two groups was statistically significant: ($P < 0.00001$). Relative risk = 0.58 (0.46, 0.74) (Figure 14).

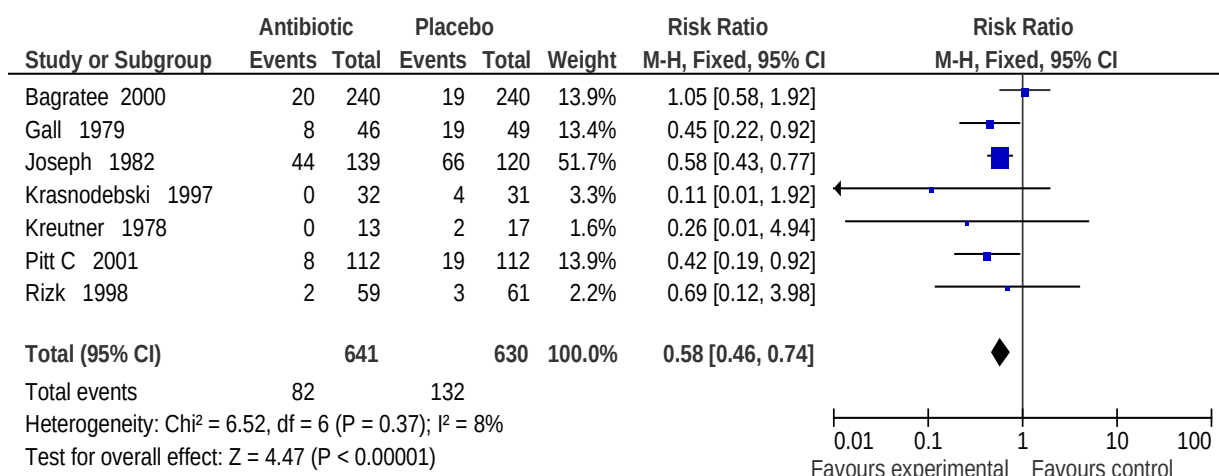


Figure 14 : Antibiotic versus placebo comparison.

In caesarean surgery, cefazolin was the most frequently used antibiotic (28.57 %); 5 trials (71.4%) concluded that antibiotics are significantly superior to placebos in SSI prevention.^{134 -138, 140}

Funnel plot: In this group, most of the studies which showed a positive antibiotic effect were those with a greater sample size. Publication bias is thus suspected (Figure 15).

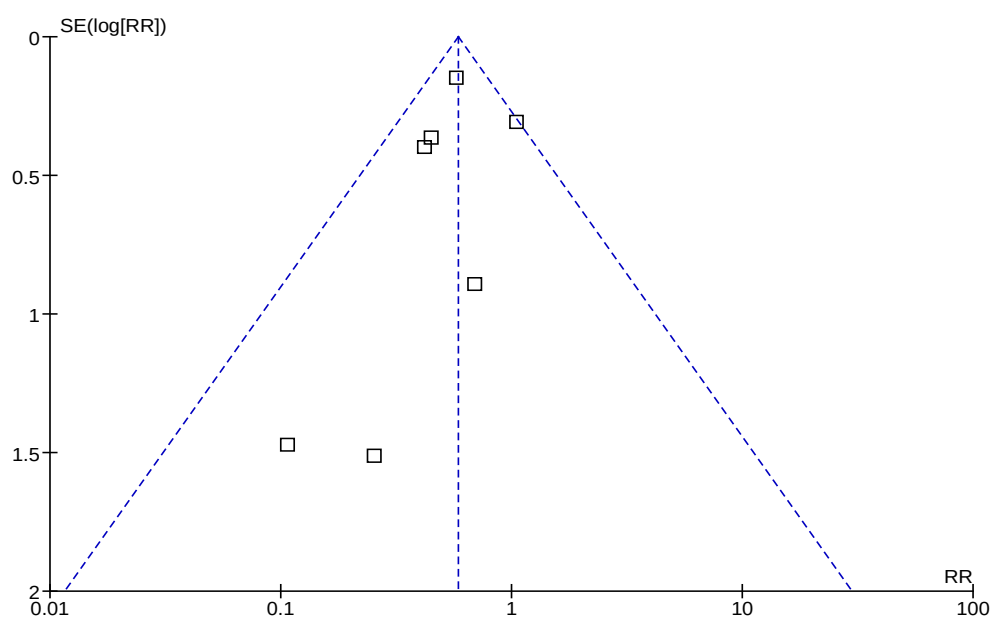


Figure 15 : Funnel Plot effect for Caesarean surgery

III-2-5 Transurethral resection of the prostate

It was found in the 4 trials concerning transurethral resection of the prostate (TURP) that there was no heterogeneity ($P=0.83$). Table 12 and figure 16 illustrate the statistical features of these two groups.

Table 12: Recapitulation of comparative trials in transurethral resection of the prostate and main results

Trial	Year	Regimen	Antibiotic Group			Placebo Group		
			N	SSI	%	N	SSI	%
Rodrigues ¹⁴¹	2004	Not specified	62	7	11.2%	62	24	38.7%
Metin ¹⁴²	2007	Cefazolin	88	14	15.9%	30	12	40%
Raz ¹⁴³	1994	Ceftriaxone	51	6	11.7%	50	20	40%
Slavis ¹⁴⁴	1992	Cefonicid	51	6	11.7%	49	18	36.7%

The difference between the two groups was also significant ($P<0.001$). Relative risk = 0.32 (0.22, 0.47) (Figure 16).

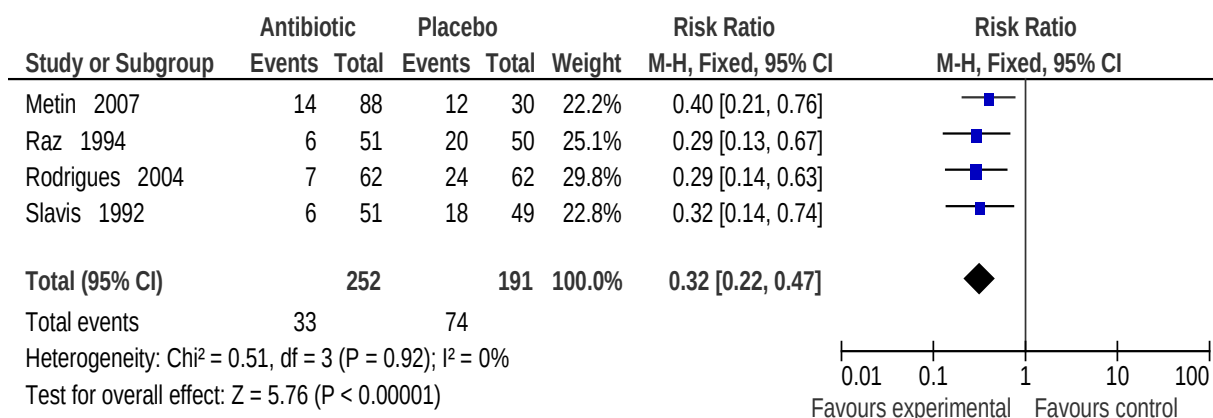


Figure 16 : Antibiotic versus placebo comparison in TURP

Cephalosporin was the most frequently used antibiotics. One trial did not specify the antibiotics used, 3 trials (75 %) show a statistically superior benefit of antibiotics compared to placebos in SSI prevention.¹⁴²⁻¹⁴⁴

Funnel plot: In this group, all the studies had small samples and demonstrate a positive antibiotic effect compared to placebos. No publication bias was suspected (Figure 17).

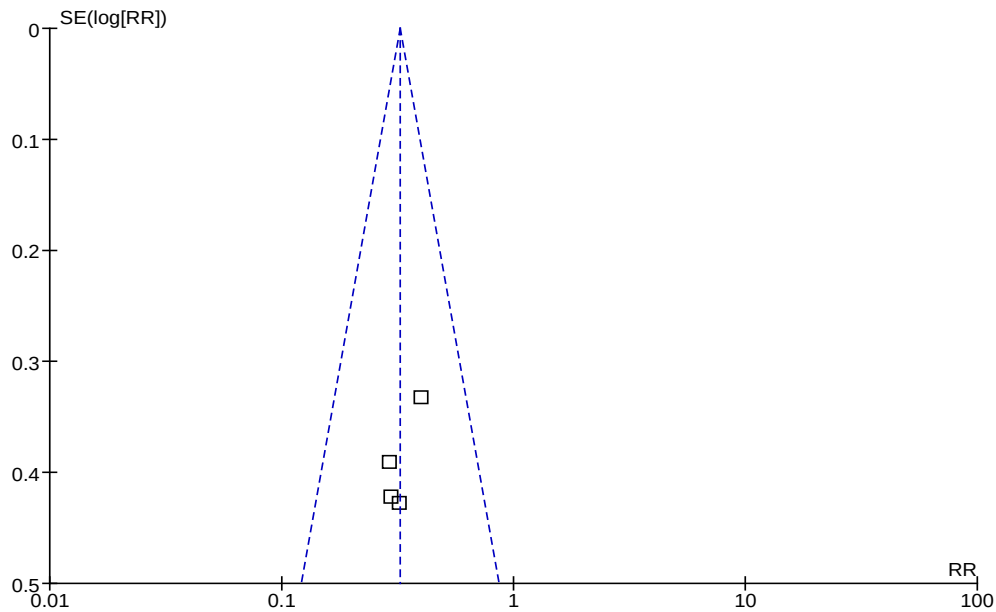


Figure 17 : Funnel Plot effect for transurethral resection of the prostate

III-2-6 Percutaneous endoscopic gastrostomy

It was found in six trials concerning percutaneous endoscopic gastrostomy (PEG) that there was no heterogeneity ($P=0.25$) (Table 13 and figure 18).

Table 13 : Recapitulation of comparative trials in percutaneous endoscopic gastrostomy procedures and main results

Trial	Year	Regimen	Antibiotic Group			Placebo Group		
			N	SSI	%	N	SSI	%
Sturgis ¹⁴⁵	1996	Cefazolin	30	4	13.3%	31	6	19.3%
Jonas ¹⁴⁶	1985	Cefoxitin	41	8	19.5%	43	28	65.1%
Jain ¹⁴⁷	1987	Cefazolin	27	2	7.4%	28	9	32.1%
Prelik ¹⁴⁸	1999	Amoxy/clav	41	8	19.5%	43	11	25.5%
Mouncher ¹⁴⁹	2003	Cefuroxime	50	1	2%	51	6	11.7%
Saadeddin ⁸⁴	2005	Amoxy/clav	51	6	11.7%	48	23	47.9%

The difference between the two groups was statistically significant: ($P < 0.001$). Relative risk = 0.36 (0.24, 0.52).

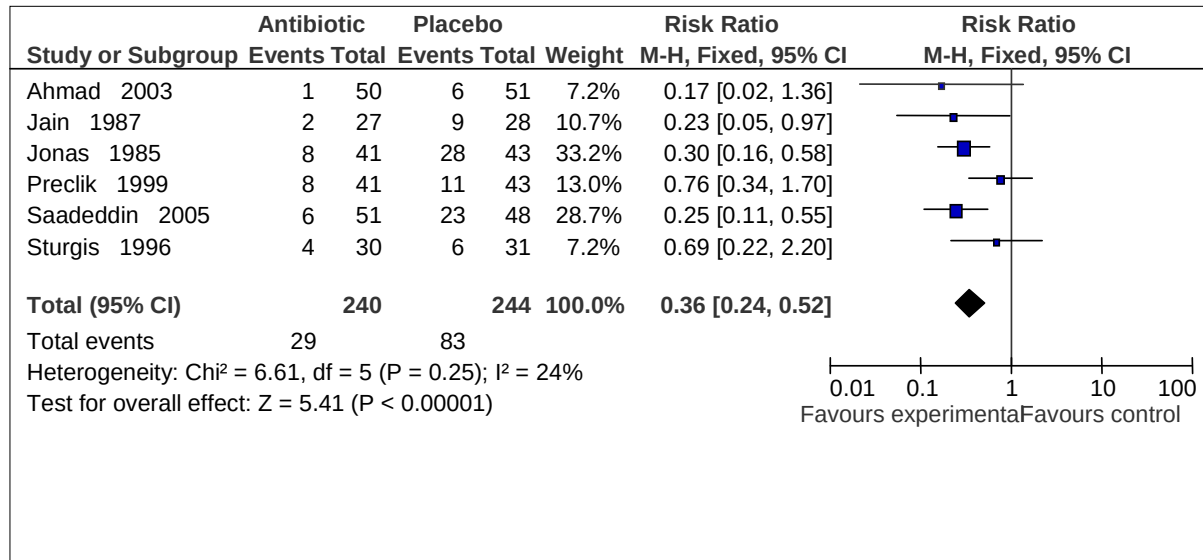


Figure 18 : Antibiotic versus placebo comparison, in PEG surgery

Cefazolin and amoxicillin combined with clavulanic acid were the most frequently used antibiotics (33.3% each). Four of the six trials (66.7%) concluded that there was an evident statistical superiority benefit of antibiotics compared to placebos in SSI prevention.

Funnel plot: this group is characterized by large sample trials with positive effects. No publication bias was suspected (Fig 19).

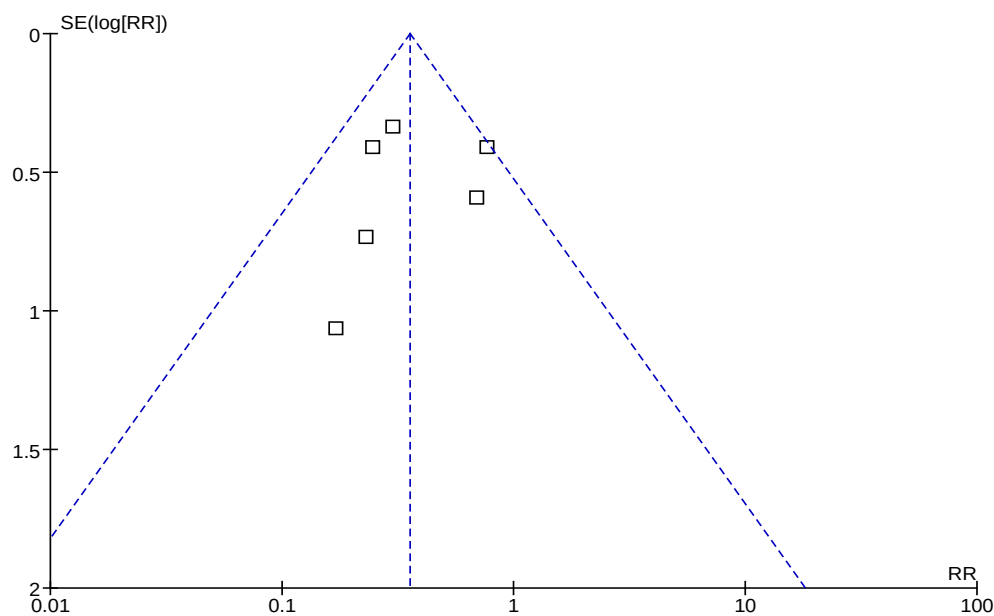


Figure 19 : Funnel Plot effect for PEG surgery

III-2-7 Hysterectomy

It was found in five trials on hysterectomies that there was no heterogeneity ($P=0.34$) (Table 14).

Table 14 : Recapitulation of comparative trials in Hysterectomy surgery,

Study	Year	Antibiotics	Antibiotic Group			Placebo Group		
			N	SSI	%	N	SSI	%
Vincelette ¹⁵⁰	1983	Metronidazol	20	3	15%	18	4	22.2%
Cubillos ¹⁵¹	2003	Tinidazol-Cefazoline	116	3	2.5%	112	18	16%
Bouma ¹⁵²	1993	Cefuroxime metronidazole	32	0	0%	28	4	14%
Karhunen ¹⁵³	1980	Tinidazole	70	1	1.4%	76	10	13.5%
Polk ¹⁵⁴	1980	Cefazolin	44	1	2%	42	10	21%

The difference between the two groups was significant ($P < 0.001$). Relative risk = 0.18 (0.09, 0.36) (Figure 20).

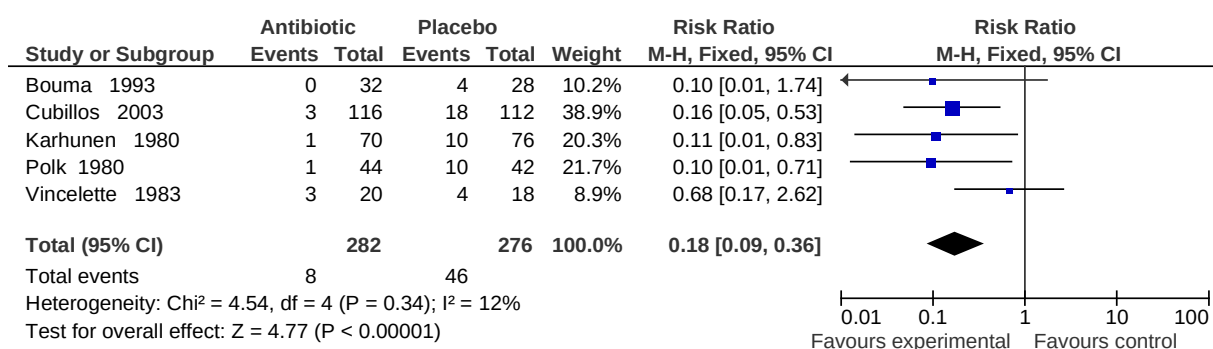


Figure 20 : Antibiotic versus placebo comparison in hysterectomy

Metronidazol and Tinidazol-cefazoline combination were the most frequently used antibiotics (33,3% each). 4 of the 5 trials (80%) concluded that there was a significant benefit of antibiotics compared to placebos in SSI prevention.¹⁵¹⁻¹⁵⁴

Funnel plot: No publication bias was suspected (Figure 21).

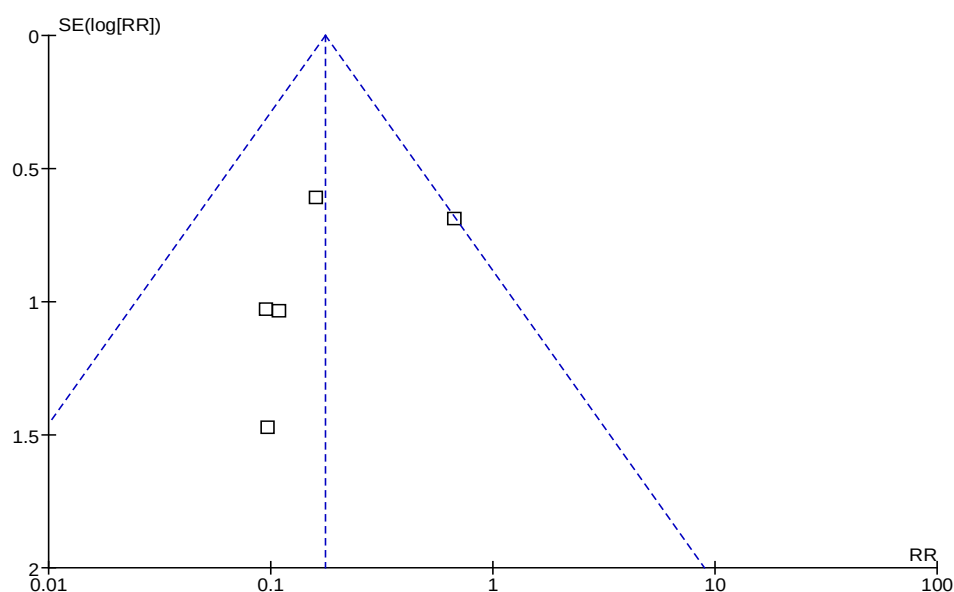


Figure 21 : Funnel Plot effect for hysterectomy

III-2-8 Orthopedic surgery

Two trials on orthopedic surgery were found to be without heterogeneity ($P=0.43$) (Table 15).

Table 15 : Recapitulation of comparative trials in Orthopaedic/ traumatologic surgery, and main results

Trial	Year	Regimen	Antibiotic Group			Placebo Group		
			N	SSI	%	N	ssi	%
Kamath ¹⁵⁵	2005	Chloramphenicol	50	4	8%	50	8	16
Kalmeijer ¹⁵⁶	2002	Mupirocin	315	1	0.30%	299	5	1,7%

The difference between the two groups was also high ($P=0.05$). Relative risk = 0.38 (0.14, 1.02) (Figure 22).

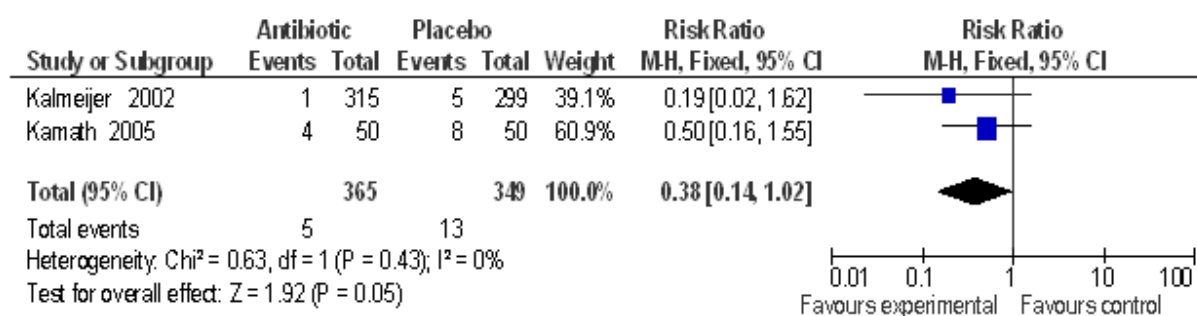


Figure 22 : Antibiotic versus placebo comparison, in orthopedic surgery

Chloramphenicol and mupirocin were used in each of the trials. The two trials concluded that there was a reduction in SSI incidence.^{124, 125}

Funnel plot: One of the two trials had a larger sample and more positive antibiotic effect than the other (Figure 23).

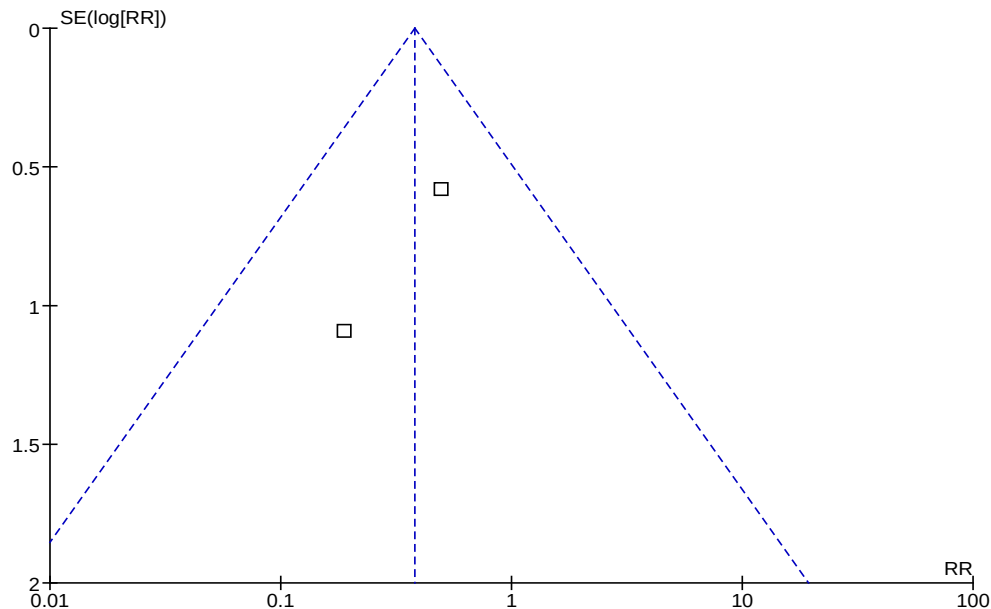


Figure 23 : Funnel Plot effect for orthopaedic surgery

III-3 DISCUSSION

III-3-1 Antimicrobial drug choice

Antibiotic use in the selected trials was generally justified and considered local bacteriological epidemiology. However, one author did not rigorously define the antimicrobial agent or the regimen to be used in his study.¹⁴¹ This author has included a total of 124 surgical procedures in his trial. Operations were performed by different surgeons, and each could choose his antimicrobial agent based on his personal preference in daily practice. Several antimicrobial regimens and different methods of administration were then used in the same trial: intravenous Gentamicin, oral Cephalothin, oral Trimethoprim/Sulfamethoxazole, oral Norfloxacin, iv Amikacin and Ceftriaxone. This study reported 7 SSI (11, 2%) in the antibiotic group, and 24 (38, 7%) in the placebo group. It is doubtful whether the results of this study can be generalized or applied in other contexts. Several audits express inappropriate antimicrobial choices and agents which do not conform to pre-established guideline recommendations.^{152, 140} The principal

concern is harmonizing and standardizing SAP practices (especially the selection process of antimicrobial regimens), curbing difficulties in the objective measurement of quantitative and qualitative effectiveness of SAP. Based on this consideration, Rodriguez's study¹⁴¹ does not seem to be sufficiently contributive.

III-3-2 Surgical Hygiene

It is well-known that 90% of surgical wounds at the moment of wound closure contain pathogenic micro-organisms, irrespective of surgical hygiene measures.¹⁵⁷ However, a strict application of surgical hygiene reduced the incidence of SSI. Very few studies among those included in this review have described preventive surgical hygiene measures that have been taken in order to minimize the additional incidence that could be due to defective surgical hygiene, in both the antibiotic and placebo groups. This description could be found only in 3 (7.32%) of the 41 trials in this review.^{159, 84, 134} The importance of surgical hygiene in SSI prevention has largely been proven. Even when surgical staff knows what must be done, hygiene measures are not always strictly respected in the pre-operative, intra-operative or post-operative periods. This mistake represents a potential source of SSI. Alexiou et al¹⁵⁸ have demonstrated a great contrast between the knowledge of theatre personnel and their daily practice in implementing surgical hygiene care to prevent SSI. It is obvious that deficiencies in pre- and post-surgical hygiene significantly increase the risk of SSI. Therefore, authors could have enhanced the credibility of their papers by describing the surgical hygiene precautions taken while conducting their studies. In the absence of this important detail, we cannot thus affirm that such measures were rigorously respected. Therefore, we cannot rationally exclude the proportion of the possible additional incidence rate of SSI which could have been caused by surgical hygiene deficiencies.

III-3-3 Surgical Site Infection Surveillance

In Part I of this review, it was mentioned that SSI can occur at any time, generally between the first and the 30th day following surgery. In one of the 41 trials, the author followed his patients only until the 7th postoperative day.¹¹⁸ A study has clearly shown the importance of post-discharge surveillance in determining the real incidence of surgical site infections.¹⁵⁹ Eriksen et al¹⁶⁰ have shown that most SSI are usually diagnosed in the post-discharge period. This author might have missed some cases of SSI among his collective patients. Rigorous SSI diagnosis can

be made only by proving micro-organism growth activity within the surgical site. Consequently, various authors have proposed defining surgical infection not only based on clinical features, but as an inflamed site with positive bacterial growth.¹⁶⁰ Only 7 (14, 29 %) authors in this review performed bacteriological examinations from the incision site.^{128, 130, 140, 142, 149, 151, 154} It is necessary to consider and admit the possibility of missing the diagnosis while assessing surgical site infections clinically without performing bacteriological examinations to determine or exclude germ growth activity. Secondly, many SSI diagnoses have been made by making a phone call to patients after hospital discharge. It seems very difficult to have total confidence in this method. The validity of the patient's recognition of signs and symptoms of SSI infection in post-discharge conditions remains debatable. These patients could have been influenced by subjective considerations which has nothing to do with SSI. Our inquietude is shared by Whitby.¹⁶² This author has concluded at the end of his study that post-discharge SSI rates determined by signs and symptoms reported by patients should be viewed with extreme caution. It is not sure that these patients were able to distinguish acute inflammation (wound healing process) from SSI. Specific education of the patients prior to hospital discharge could have been conducted by investigators. This measure may have increased the efficiency of this process. To avoid this bias, some of our authors have systematically invited their patients to attempt additional medical consultations, in order to conduct an appropriate physical examination to detect and treat SSI.

III-3-4 Etiology of Surgical site infection

The potential importance of MRSA and fungal infection in the incidence of SSI has been clearly shown in Part I of this thesis. Etiological investigation was very rare in our trials. One of the 41 trials only suspected etiology other than bacterial, without precisely determining the organism.¹¹⁵

III-3-5 Methicillin-resistant *Staphylococcus aureus* (MRSA)

The role of MRSA is clearly defined in the physiopathology of SSI. Postoperative maneuvers are the factors which most often create conditions favourable for the occurrence of SSI, owing to MRSA. Walls et al¹⁶³ have shown that methicillin-resistant *S. aureus* has become a prominent cause of SSI in hip replacement. Studies have also shown increased MRSA etiology in SSI.^{164,165} Sankar et al¹⁶⁶ have shown that, if a systematic screening of the patient is performed at the moment of hospital entry, it could significantly reduce the incidence of SSI. Farrin et al¹⁶⁷ have

retrospectively studied patients with surgical site infections who underwent surgery, in order to compare patients infected with MRSA with those infected with other organisms. He found that 77 (28.5%) of the 270 patients had cultures that yielded MRSA. This is proof that MRSA now play a potentially important role in SSI etiology. No trial in this review has performed systematic screening for MRSA. Postoperative care has not been described; we cannot thus formally exclude that MRSA could have played a role in the increasing SSI incidence rate in many of the 41 included trials. Systematic MRSA screening should be conducted to reduce the SSI incidence rate and thus increase the efficacy of SAP.

III-3-6 Fungal Infection

Fourteen trials out of the 41 in this review did not perform a fungal investigation exam. The 27 other trials did not either mention fungal infection as a possible SSI aetiology. None of the antimicrobial regimens listed in this review comprised antifungal drugs. However, the antibiotics used for the prevention of the bacterial infections are not effective for fungal infection. If we consider this potential responsibility of fungal infections as a probable cause of SSI, we cannot rigorously affirm that the increased incidence of the SSI is entirely due to the inefficiency of SAP. If the possibility of fungal infection is not considered, this will not be effectively covered by the choice of antibiotic, and thus there is a risk of increasing the rate of SSI. Thus, a proper SSI prevention should protect against fungal infection, particularly, in immuno-compromised patients and in some types of surgery like gastrostomy, not only in solid organ transplantation where SSI caused by fungi are known to be associated with the highest mortality rates.¹⁶⁸

III-3-7 Risk factors related to SAP

SAP practice involves two systems: bacterial contamination, and on the other hand, the resistance of the host. SAP then consists of reinforcing the defensive capacities of the host to enable him to better resist to microbial invasion. Most factors reduce defense capacities of the host and impose particular SAP measures. Some of the most important of those risk factors are HIV infection and smoking habits.

III-3-8 HIV infection

3 studies out of the 41 did not exclude patients with HIV: ^{118, 122, 142} This omission undoubtedly could affect their results. Pan et al ¹⁶⁹ have shown increasing numbers of HIV-positive patients among those receiving surgical treatment. Boukinda et al ¹⁷⁰ have shown a prevalence of 20, 9% HIV positive patients out of 129. Martinson et al ¹⁷¹ have found a HIV prevalence of 32.8% out of 1000 patients receiving surgical treatment. Pan et al ¹⁶⁹ established that HIV- infected patients have a significant risk for SSI. The fact of not excluding the HIV positive patients has undoubtedly influenced the results of these authors.

III-3-9 Smoking

13 authors out of 37 formally did not exclude smokers; however, the risk of SSI among smokers is raised. Kamath et al ¹⁵⁵ sufficiently highlight the role that smoking plays as a risk factor for SSI. In his study, smoking was found to be the only factor that was significantly associated with SSI.

III-3-10 Tension free-mesh inguinal hernia repair

Most of the individual trials in this review could not establish a significant statistical difference between SAP and placebo in the reduction of SSI in the tension free-mesh inguinal hernia repair. In the early period of the use of prostheses in hernia repair procedures, it was believed that the simple fact of inserting mesh prosthesis increased the risks of SSI. SAP was therefore considered as an obligatory preventive measure. However, the many studies thereafter could not confirm this fear. Even though intuition forces us to recognize that an important potential risk lies in the simple presence of prosthesis, which is a foreign body. The most eloquent case is the study that has been conducted by Yerdel et al. ¹¹⁹ In 120 patients who have benefited from hernia surgery with a mesh establishment, the use of routine prophylactic antibiotics resulted in no SSIs. Since there is a significant heterogeneity in this group, it is not easy to interpret these results. There is no strong scientific evidence to support a policy of systematic antimicrobial prophylaxis in this surgical procedure. ¹¹⁸ Systematic use of prophylactic antibiotic in patients receiving tension free-mesh inguinal hernia repair cannot thus be recommended.

III-3 -11 Endodontic surgery

The need for systematic SAP in endodontic surgery remains scientifically debatable, although it is well-known in practice that risks of gingivitis and endocarditis are associated with endodontic

procedures. The use of prophylactic antibiotics in endodontic surgery is still empirical and not supported by any scientific basis. Thus, international guidelines do not recommend SAP in this type of surgery. Studies carried out in USA by Yingling et al,¹⁷² however, show that in spite of the absence of SAP recommendation, 37% of surgeons routinely prescribed prophylactic antibiotics for endodontic surgery. Our results follow this tendency: despite the fact that the majority of the trials included for endodontic surgery in this review have demonstrated obvious benefits of antibioprophylaxis, our investigation found an insufficiently significant benefit of antibiotics compared to the placebo group. In light of this result, it cannot be concluded whether systematic SAP is to be recommended in patients receiving endodontic surgical treatment. Future publication of studies on this topic will need to occur in a manner which eliminates the current publication bias.

Aside from this, when considering the potential cardiac complications associated with this type of procedure, it could be advisable to recommend SAP for high-risk patients. In such cases, the combination of Amoxicillin and clavulanic acid would be the preferable choice.

III-3-12 Caesarean section

The current recommendation in caesarean section procedures is to administer a systematic iv Cefazolin after cord clamping. This has been shown to significantly reduce the incidence of SSI. A recent study has shown that administration of cefazolin prior to skin incision is superior to Cefazolin administration at the time of cord clamping in preventing post-caesarean surgical site infection complications.¹⁷³ Meanwhile, Wax's study¹⁷⁴ shows that in preventing post-Caesarean infections, 1 g of Cefazolin administered preoperatively is no more effective than the same dose administered after cord clamping. However, more important than these contradictory results is the need to consider the main risk of this method before cord clamping, i.e. the possible transplacental passage of certain antibiotics to the foetus. Otherwise, the benefit of SAP after cord clamping in Caesarean sections has largely been demonstrated. Our results largely confirm this. Therefore, a systematic SAP can be recommended in gynecological and obstetric surgery, but preferably after cord clamping, owing to the risk of transplacental passage described above. iv Cefazolin can be recommended for this purpose.

III-3-13 Transurethral resection of the prostate

Scientific literature reports that no controlled study could clearly show any benefits, nor could the strict need for SAP in simple TURP be demonstrated. Several studies have consolidated the idea that SAP is not necessary in transurethral resection of the prostate. Otherwise, Scholz et al.¹⁷³ have shown that 1g of intravenous Ceftriaxone is effective in preventing SSI in patients undergoing TURP, but Rodrigues¹⁴¹ has obtained less optimistic results. For him, SAP for TURP remains debatable. On the other hand, the former authors affirm that systematic antibiotic use in transurethral resection of the prostate is irrational. The value of the methodology of his study appears debatable, as the antibiotic regimens were not standardized, the choice of the antimicrobial agent depended on each surgeon and the patients were not operated by the same surgical team. All this calls into question the results obtained by this author. As we saw in the second chapter of this thesis, SAP diagnosis is usually a clinical matter. Urological surgery is particular in that the diagnosis of the SSI, for reasons of physical accessibility, cannot be made clinically by direct observation. It is thus generally done indirectly through seeking the presence of micro-organisms in the urine. However, this process itself is debatable. The current study considered that this process has its place, and is even more objective than the clinical diagnosis. This position is concordant with Surin et al,¹⁶¹ who propose that the insulation of a micro-organism eliminates the criteria of definition of a SSI. The correlation which exists between the post operative bacteria and SSI cannot be questioned. The five consulted studies affirm that there is an interest in using a systematic antibioprophylaxis in TURP. They established, in particular, the benefit of this practice compared to placebo therapy. The current study noticed that the rate of SSI among patients who received placebo therapy were high. On this basis, the current study concurs with these authors in recommending the systematic practice of administering antimicrobial prophylaxis for transurethral resection of the prostate. Considering moreover that this type of surgery is generally carried out on older people who generally present co-morbidities that increase the risk of infection (in particular diabetes mellitus), first-generation cephalosporin antibiotics can be used.

III-3-14 Percutaneous endoscopic gastrostomy

Besides SSI, other infectious complications can occur after PEG, such as pneumonia. Most commonly, peritonitis.¹⁷⁴ The role of fungal infection in PEG is well established.¹⁷⁶ Pneumonia and peritonitis are very severe, and can result in a high mortality rate. SSI has been reported in

occur in 30 % of fatal cases of pneumonia and peritonitis. This review did not find a statistically significant difference between the antibiotic and placebo groups ($P=0.25$). The need of SAP in PEG seems difficult to prove indeed. This is why some authors do not recommend antimicrobial prophylaxis in this procedure ¹⁴⁶. In light of these results, we cannot recommend systematic antibiotic prophylaxis in PEG. This preventive measure should be reserved for patients at a high risk of SSI.

III-3-14 Hysterectomy

It is interesting to examine the trials of Cubillos ¹⁵¹ who tests the effect of oral Tinidazol administered simultaneously with a vaginal Myconazol-tinidazol in patients who have already received preoperative intravenous Cefazoline in both groups. It is not easy to evaluate the real benefit that this study brings in the field of the knowledge about surgical antimicrobial prophylaxis: What is the contribution of Cefazoline that each patient has received at the beginning? What is the part of the additional Imidazole in the prevention of the SSI risk? In this type of surgery, the SARF recommends 2g of preoperative Cefazoline alone, while the Quebec Medicine/Drug Council recommends 1g intravenous Céfazoline, at the induction of anaesthesia. ¹⁷⁸ The UHG ¹⁷⁸ does not recommend an antibioprohylaxis in this case.

Only two trials in this review found a statistically significant difference between the antibiotic and placebo groups in preventing SSI incidence. However, this meta-analysis did not show a significant difference between the antibiotic and placebo groups ($P=0.34$). SSI has been reported to occur in about 10% to 30% ¹⁷⁹ of hysterectomies even when prophylactic antibiotics have been administered before the procedure. Hysterectomy can thus be considered as a type of surgery presenting a high risk of infection. Abstention from SAP practice will increase the already significant risk of SSI occurrence. Incidence of SSI is greater in vaginal hysterectomies than in abdominal hysterectomies (6% to 25% versus 4% to 10%). Based on these considerations, it appears reasonable to recommend a systematic SAP in vaginal hysterectomy and in high-risk abdominal hysterectomy. The gold-standard molecule should be a combination of IV Tinidazole and Cefazolin.

III-3-15 Orthopedic and traumatologic surgery

Controlled trials comparing antibiotic to placebo in orthopaedic and traumatologic surgery are not easy to find in scientific literature. There are two reasons for this. Firstly, we should consider that orthopedic surgery is a potential source of post-surgical site infection. It is indeed well-established that orthopedic surgery is associated with a very great risk of deep and late SSI in joints.¹⁸⁰ The second reason is that some researchers consider that antibiotic versus placebo trials cannot easily be applied to bone surgical procedure (this is considered by some researchers as an unethical methodology because of the potential gravity of bone infections)^{181, 182} when considering the difficulty of treating a post surgical osteitis or osteomyelitis. These two reasons justify the particularly rigorous preventive measures that are taken by orthopedists in terms of surgical hygiene and antibiotic prophylaxis. We could thus find only two trials: one testing the nasal Mupirocin ointment to prevent SSI due to *S. aureus*, and the second using Chloramphenicol ointment with the same goal. It is important to note that in the two trials, patients already had received systemic antibiotics. Therefore, these trials were interested in studying the additional benefit that topical and local antibiotic can bring in the process of reducing SSI. We have demonstrated a highly significant difference between the two groups, in favour of the antibiotic ($P=0.043$). A similar test has already been performed in ophthalmological surgery, with similar results. Thus, a systematic topic and/or local antibiotic can be beneficially applied, in addition to classic antibioprohylaxis coverage in bone surgery.

III-4 Conclusion

The aim of this thesis was to try to explain why the rate of SSI is very high. This review has established a correlation between a poor implementation of the cardinal principles of SAP and the probable effects on its effectiveness. Subsequently, it has shown by means of a systematic review of RCTs that results available in surgical literature do not always reflect reality, because of problems related mostly to methodology and possible publication bias. These results are sometimes over-estimated, and sometimes under-estimated. SAP remains effective overall, but not sufficiently when compared to the potentialities revealed by this important preventive measure. SAP could offer us even more if it is put into practice with due consideration for standards and principles. RCTs comparing SAP to placebo therapy could offer more optimistic results if the methodology of future studies is more rigorous. Throughout this thesis, it is shown

that potential and substantial possibilities of improving this effectiveness exist. We consider that poor implementation of SAP principles is an important cause of the high incidence rate of SSI.

Part IV

RECOMMENDATIONS

Based on the findings of this review, the following recommendations can be made:

- 1- To look for a strategy in order to discourage SAP practice which is carried out without a comprehensive risk assessment. Useless associations of several antimicrobial agents should also be discouraged.
- 2- To improve compliance of surgeons with guideline recommendations, particularly with regard to the timing and duration of antimicrobial administration.
- 3- To practice antimicrobial restriction on the double qualitative and quantitative level, in order to favor appropriate antimicrobial selection and prevent prophylactic antibiotic abuse. This restriction policy could be advantageously implemented by hospital pharmacies, which are in charge of the management and control of drugs used in hospital milieu.
- 4-To consider the potential role of fungal infections when elaborating guideline recommendations for SAP, especially in immuno-compromised patients.
- 5- Post-discharge surveillance of SSIs should be adopted as a routine by hospital infection control committees in order to improve health-care quality through the detection of risk factors and intervention outside medical centers. Studies on intervention measures are urgently needed.

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