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DOI: https://doi.org/10.1016/s1010-7940(00)00469-3

ELSEVIER

European Journal of Cardio-thoracic Surgery 18 (2000) 440–446

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Review article

Evolution of antimicrobial prophylaxis in cardiovascular surgery

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Received 29 December 1999; received in revised form 20 April 2000; accepted 26 April 2000

Abstract

Objective: To examine the optimal duration of antibiotic prophylaxis in major cardiovascular surgery. **Methods**: In the past 15 years, four prospective randomized, controlled studies, conducted by the same group of authors, compared seven prophylactic antimicrobial regimens in 2970 patients undergoing major cardiovascular surgery. In 1980/81, a 4-day cefazolin (CFZ) prophylaxis was compared with a 2-day cefuroxime (CFX) administration ($n = 566$). In 1982/83, a 2-day CFX prophylaxis was compared with a two shot ceftriaxone (CRO) prophylaxis ($n = 512$). In 1984/87, a 1-day CFZ prophylaxis was compared with a single shot prophylaxis of CRO ($n = 883$). In 1994/1995, a 4 day combination of amoxicillin (AM) and netilmicin (NET) prophylaxis was compared with a single shot prophylaxis of CFX ($n = 1009$). **Results**: Total infection rate varied between 4.5 and 5.7%, despite different antimicrobial regimen used and their varying duration. Wound infection rate was 1.1% (range 0.4–2.5%), sepsis rate was 0.8% (range 0.4–1.6%), pneumonia rate 2% (0.7–2.9%), urinary tract infection rate 0.4% (range 0–1.4%), and central venous catheter-related infection rate was 0.4% (0–1%). The 30-day mortality rate was 1.3% (range 0.4–2%). All these differences were not statistically significant. **Conclusions**: A low infection rate (range 4.5–5.7%) occurred despite changes in duration of various prophylactic antibiotic regimen with cephalosporins of first, second or third generation. As a single shot prophylaxis could nowadays successfully be used in cardiovascular surgery, no postoperative antibiotics should be used, unless an intraoperative or a postoperative infection is documented or in presence of major perioperative complications.

Keywords: Cardiovascular surgery; Antibiotic prophylaxis; Cefazolin; Cefuroxime; Ceftriaxone; Amoxicillin; Netilmicin

1. Introduction

Prophylactic antibiotics have been used in cardiovascular surgery for several years, in order to reduce the risk of postoperative infections [1,2]. The initial long duration of antimicrobial administration was progressively shortened. In the late 1970s, duration of the antimicrobial regimen given as prophylaxis (cefazolin 4×0.5 g/day, i.v.) has decreased from 7 to 4 days safely. In the following years, seven different antimicrobial regimen with different duration, progressively shorter, (4 days vs. 2 days, 2 days vs. 2 doses, 1 day vs. 1 dose, 4 days vs. 1 dose) were compared in prospective randomized trials by one of the authors (S.G.).

Aim of this study was 'meta-analysis' of four consecutive trials dealing with antibiotic prophylaxis in cardiovascular surgery. Main goal of this study was to evaluate the effect of reduction of antibiotic prophylaxis in postoperative infectious complications.

2. Patients and methods

Between 1980 and 1995, four randomized studies compared seven different perioperative prophylactic antimicrobial regimen in major cardiovascular surgery. The first three studies were performed at the University Hospital of Zurich, the last one at the Onassis Cardiac Surgery Center, in Athens. The procedures followed were in accordance with the Helsinki declaration.

Between September 1980 and July 1981, a 4-day cefazolin (CFZ) prophylaxis (4×0.5 g/day, i.v.) was compared with a 2-day cefuroxime (CFX) administration (2×1.5 g/d, i.v.). Of 569 patients who entered the study, 281 received CFZ and 285 CFX [3]. Between May 1982 and March 1983, a 2-day CFX prophylaxis (4×1.5 g/day, i.v.) was compared with a two shot ceftriaxone (CRO) prophylaxis (2 g plus 1 g 24 h later, i.v.). Of 523 patients enrolled, 258 received CFX and 254 CRO [4]. Between November 1984 and March 1987, a 1-day CFZ prophylaxis (4×0.5 g, i.v.) was compared with a single shot prophylaxis of CRO (1×2 g, i.v.). Of 883 patients enrolled, 439 received CFZ and 444 CRO [5]. Between May 1994 and April 1995, a 4-day amoxicillin (AM) plus netilmicin (NET) prophylaxis (3×2 g + 2×150 mg/day, i.v.) was compared

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1010-7940/00/$ - see front matter
PII: S1010-7940(00)00469-3

with a single shot prophylaxis of CFX (1 × 3 g, i.v.). Of 1009 patients enrolled, 508 received AM-NET and 501 CFX [6].

All patients aged over 16 years undergoing open heart surgery or major vascular surgery were eligible for trial entry (except the fourth study where no major vascular surgery was included except thoracic aorta aneurysms).

All patients with preoperative infection, those who had received any antibiotic within 48 h prior to operation and those with known allergy to β-lactamic antibiotics were excluded from the study protocol.

Patients were allocated to one of two treatment groups by means of a randomized code, stratified for cardiac and major vascular operations. The first dose was always given prior to surgery, just prior the induction of anesthesia. Treatment groups were well matched for age, sex, weight, height and type of surgical procedure in all studies. There were no statistically significant differences in co-morbid conditions, such as history of diabetes mellitus and/or renal failure and/or chronic obstructive pulmonary disease (COPD), obesity, and prolonged preoperative hospitalization between groups among these four trials included. In addition, there were no differences between groups regards to bleeding requiring re-exploration. In these studies, there were no patients who underwent coronary artery bypass grafting with bilateral mammary artery. In all patients who received a single shot of antibiotic prophylaxis, regimen was administered just prior the induction of anesthesia. In this case, no additional dosage was administered in the pump priming solution, as well as in patients with a prolonged duration of extracorporeal circulation.

Hematological tests, liver function tests, serum creatinine and urea were measured preoperatively. These measurements were repeated daily during the ICU period, one week after and/or immediately before discharge. Chest X-rays were taken before, immediately after the operation, 1 and/or 2 days later prior to leaving hospital and in between when clinically indicated. Body temperature was measured every 1 or 2 h during the ICU period and in the ward at least twice daily. Surgical wounds were examined daily and swabs of any secretions or pus were taken for bacteriological examinations. Central venous catheters remained in the majority of patients one day. In patients with prolonged ICU length of stay, all central catheters changed in case of suspicion of central venous catheter-associated infection or sepsis. Swan–Ganz catheters were removed prior to the fourth postoperative day. Postoperative infections were treated with appropriate antibiotics and when needed, surgical intervention.

2.1. Definitions

Wound infection was defined as purulent secretion with growth of bacteria, classified into mild (purulent discharge only), moderate (discharge of pus plus constitutional upset) and severe (requiring active surgical intervention such as reoperation) [7]. Urinary tract infection was defined as clinical signs of infection in combination with urine cultures demonstrated a pathogen numbering $>100\ 000$ c.f.u. ml^{-1} [8].

The diagnosis of pneumonia in the first three studies was made when three of the following criteria were present: purulent sputum, rales, fever, and positive chest X-ray. In the last study, two more criteria were added: leukocytosis, and positive culture. Diagnosis was made when four out of six criteria were present [9].

The patients were defined as having sepsis if they manifested the following: (1) at least two of the following criteria: (a) body temperature >38°C, (b) WBC counts $>12 \times 10^9$/l or $<4 \times 10^9$/l or immature neutrophils $>10\%$, (c) heart rate >90 beats/min, and (d) respiratory rate >20 breaths/min or P_aCO_2 <32 mm Hg; (2) a documented bacteremia [10].

Chest X-rays, blood cultures and urine sedimentation tests were negative in patients with fever (>39°C) of unknown origin.

2.2. Demographic data

The randomization in each study produced groups with well-matched demographic data (Table 1).

2.3. Surgical procedures

A total of 3122 patients entered the four studies. Of these, 152 were excluded for various reasons. Out of 2970 patients examined, 2708 underwent open heart surgery and 262 major vascular surgery (Table 1). The majority of operations were aortocoronary artery bypass grafting ($n = 1822$, 61.3%) with an increased trend during this period, followed by valve replacement ($n = 739$, 24.9%), associated with a decreased trend. Surgery of major arteries with implantation of a vascular prosthesis accounted for 262 (8.8%) operations. The remaining 147 (4.9%) were other operations with use of cardiopulmonary bypass (PCB). In all studies, both groups were well matched for the type of operation (Table 1).

2.4. Statistical analysis

Values are presented as mean ± SD or numbers and percentile. A P-value less than 0.05 was considered statistically significant.

3. Results

3.1. Infection rate

Wound infection developed in 33 patients (1.1%, range 0.4–2.5%). There were 17 severe sternal wound infections that required reoperation, six moderate sternal wound infections, three moderate inguinal wound infections and seven mild or moderate donor site wound infection (Table 2). Patients with sternal wound infections had prolonged opera-

Table 1
Demographic data and surgical procedures[a]

	1980–81			1982–83			1984–87			1994–95		
Regimen (duration)	CFZ (4 days)	CFX (2 days)	*P*	CFX (2 days)	CRO (2 doses)	*P*	CFZ (1 day)	CRO (1 dose)	*P*	CFX (1 dose)	A-N (4 days)	*P*
n	281	285		258	254		439	444		501	508	
Gender (M/F)	214/67 (76%/24%)	234/51 (82%/18%)	0.1	215/43 (83%/17%)	206/48 (81%/19%)	0.6	384/55 (87%/13%)	390/54 (88%/12%)	0.9	431/70 (86%/14%)	430/78 (85%/15%)	0.6
Age (years)	53.2 ± 11.4	53.4 ± 9.7	0.8	55.4 ± 11.9	55.5 ± 12.4	0.9	56.7 ± 10.8	57.1 ± 12.9	0.6	59.8 ± 8.8	59.9 ± 9.4	0.8
Weight (kg)	69.1 ± 14.1	68.9 ± 12.7	0.8	70.3 ± 9.6	71.8 ± 12.3	0.1	71.5 ± 11.0	72.4 ± 14.0	0.3	76.6 ± 7.1	76.2 ± 6.4	0.3
Height (cm)	171 ± 9.8	170 ± 10.5	0.2	169 ± 9.7	170 ± 10.5	0.3	170 ± 10.9	170 ± .9.7	1	169.8 ± 5.5	169.7 ± 5.9	0.7
Type of surgery												
CABG	130 (46%)	132 (46%)	0.9	118 (46%)	130 (51%)	0.2	231 (53%)	236 (53%)	0.9	429 (86%)	416 (82%)	0.1
Valve replacement[b]	105 (37%)	105 (37%)	0.9	83 (32%)	72 (28%)	0.4	119 (27%)	127 (29%)	0.7	52 (10%)	76 (15%)	0.2
Other operation[c]	20 (7.1%)	18 (6.3%)	0.8	9 (3.5%)	6 (2.4%)	0.6	29 (6.6%)	29 (6.5%)	0.9	20 (4.0%)	16 (3.1%)	0.5
Aorto-femoral	21 (7.5%)	25 (8.8%)	0.7	45 (17%)	45 (18%)	0.9	40 (9.1%)	37 (8.3%)	0.7	0 (0%)	0 (0%)	–
Other grafts	5 (1.8%)	5 (1.7%)	0.7	3 (1.2%)	1 (0.4%)	0.6	20 (4.5%)	15 (3.4%)	0.4	0 (0%)	0 (0%)	–

[a] Data are presented as mean ± SD or no. (%). CFZ, cefazolin; CFX, cefuroxime; CRO, ceftriaxone; A-N, amoxicillin + netilmicin.
[b] Including combined operations of valve replacement plus CABG.
[c] Other operations in cardiopulmonary bypass.

Table 2
Rates of nosocomial infection, mortality, and of hospitalization[a]

Regimen	1980–81				1982–83				1984–87				1994–95			
	CFZ (4 days) ($n = 281$)	CFX (2 days) ($n = 285$)	P	95% CI	CFX (2 days) ($n = 258$)	CRO (2 doses) ($n = 254$)	P	95% CI	CFZ (1 day) ($n = 439$)	CRO (1 dose) ($n = 444$)	P	95% CI	CFX (1 dose) ($n = 501$)	A-N (4 days) ($n = 508$)	P	95% CI
	n (%)	n (%)			n (%)	n (%)			n (%)	n (%)			n (%)	n (%)		
Wound infection	7 (2.5)	3 (1.1)	0.3	− 0.007, 0.035	3 (1.2)	3 (1.2)	0.6	− 0.018, 0.018	2 (0.4)	6 (1.3)	0.2	− 0.017, 0.005	3 (0.6)	6 (1.2)	0.4	− 0.017, 0.005
Sepsis	1 (0.4)	2 (0.7)	0.5	− 0.017, 0.030	4 (1.6)	4 (1.6)	0.7	− 0.021, 0.021	5 (1.1)	5 (1.1)	0.7	− 0.013, 0.013	2 (0.4)	1 (0.2)	0.6	− 0.015, 0.013
Pneumonia	4 (1.4)	7 (2.5)	0.5	− 0.033, 0.013	5 (1.9)	5 (1.9)	0.7	− 0.024, 0.024	9 (2.0)	3 (0.7)	0.1	− 0.004, 0.029	13 (2.6)	15 (2.9)	0.9	− 0.020, 0.018
UTI	4 (1.4)	3 (1.1)	0.9	− 0.014, 0.022	0 (0)	0 (0)	1	–	1 (0.2)	0 (0)	0.9	− 0.002, 0.006	3 (0.6)	0 (0)	0.3	− 0.001, 0.001
Central venous catheter-related infection	0 (0)	0 (0)	1	–	0 (0)	0 (0)	1	–	2 (0.4)	1 (0.2)	0.9	− 0.002, 0.010	5 (1.0)	5 (1.0)	1	–
Endocarditis[b]	–	–	–	–	–	–	–	–	–	–	–	–	2 (0.4)	1 (0.2)	0.6	− 0.015, 0.013
Other infection	0 (0)	0 (0)	1	–	0 (0)	0 (0)	1	–	0 (0)	0 (0)	1	–	0 (0)	1 (0.2)	0.9	− 0.014, 0.010
Multiple infections	–	–	–	–	–	–	–	–	3 (0.7)	5 (1.1)	0.7	− 0.016, 0.008	–	–	–	–
Total infections	16 (5.7)	15 (5.3)	0.9	− 0.033, 0.041	12 (4.7)	12 (4.7)	1	− 0.037, 0.035	22 (5.0)	20 (4.5)	0.8	− 0.023, 0.033	28 (5.6)	29 (5.7)	0.9	− 0.030, 0.026
Hospitalization (days)	10.5 ± 3.1	10.1 ± 3.9	0.2	− 0.18, 0.98	9.5 ± 2.4	9.9 ± 2.8	0.08	− 0.85, 0.05	9.6 ± 2.7	9.5 ± 1.9	0.5	− 0.210, 0.410	9.3 ± 2.8	9.5 ± 3.1	0.2	− 0.570, 0.170
Mortality (30 days)	3 (1.0)	4 (1.4)	0.9	− 0.022, 0.014	3 (1.2)	2 (0.8)	0.9	− 0.012, 0.020	6 (1.3)	2 (0.4)	0.3	− 0.003, 0.021	8 (1.6)	10 (2.0)	0.8	− 0.020, 0012

[a] Data are presented as mean ± SD or n (%). CFZ, cefazolin; CFX, cefuroxime; CRO, ceftriaxone; A-N, amoxicillin + netilmicin.
[b] In the first 3 studies, endocarditis was incorporated in the septic group.

tion times (>120 min.) and major perioperative complications or they were re-explorated because of bleeding.

Sepsis developed in 24 patients (0.8%, range 0.4–1.6%). Pneumonia developed in 61 patients (2%, range 0.7–2.9%). Urinary tract infections occurred in 11 patients (0.4%, range 0–1.4%). Central venous catheter-related infection developed in 13 patients (0.4%, range 0–1%). Fever of unknown origin occurred in 87 patients (2.9%).

Total postoperative infection rate was 5.2% (range 4.5–5.7%) (Table 2). There were no statistically significant differences regards to kind of infection between various regimen. Infection rate did not vary significantly during this period, while the duration of the regimen became progressively shorter.

Isolated pathogens for all studies are shown in Table 3. There was no statistically significant difference between the various regimen in the occurrence of Gram positive cocci and Gram negative rods. In contrast, there was a difference in the occurrence of Gram positive cocci and Gram negative rods regarding the type of infection. Pathogens isolated from infected wounds were mainly Gram positive cocci while those isolated from other infections like pneumonia or urinary tract infections were Gram negative rods.

3.2. Biochemical measurements

There were no significant differences in the pre-treatment or follow-up biochemical measurements. All minor changes observed were not clinically significant and they were not related to administered antibiotics. There were no side effects reported in these studies, except two cases of diarrhea due to *Clostridium difficile*. Being overt infections in the postoperative period, they were classified as infections and not as side effects.

3.3. Hospital stay

During this period, a light decrease of hospital length of stay was observed from 10.5 to 9.3 days (Table 2).

3.4. Mortality

A total of 38 patients (1.3%) died within a month. For 25 patients, main cause of death was cardiogenic shock, for seven patients cause of death was multiple organ failure, while in six patients (0.2%), death was exclusively due to a severe infection. Of these six patients, nosocomial pneumonia was the main cause of death in three patients and sepsis in the remaining three ones.

4. Discussion

Postoperative infection following cardiovascular surgery is a serious and often life-threatening complication [11,12]. It is associated with a substantial morbidity, prolonged hospital stay and an increasing hospital cost.

Prophylactic antibiotics have been used for several years in order to reduce the risk of postoperative infections [1,2]. Cephalosporins are frequently used because of their broad spectrum of activity and low degree of toxicity [13]. However, the number of resistant microorganisms is increasing, particularly the β-lactamase producing gram-negative organisms capable of destroying many penicillins and cephalosporins [14].

The reason for the development of resistant strains is probably the long-term application of antibiotics. The shortest effective treatment will be therefore of advantage [15]. An effective prophylactic regimen should be directed against the

Table 3
Isolated microorganisms[a]

Microorganism	1980–81		1982–83		1984–87		1994–95		Total
	CFZ	CFX	CFX	CRO	CFZ	CRO	CFX	A-N	
Staphylococcus (coagulase negative)	2	2	2	3	7	13	6	9	44
Staphylococcus aureus	1	4	1	2	8	5	8	6	35
Enterococcus	1	1	2	3	3	1	0	0	11
Enterobacter	2	1	2	2	2	4	3	2	18
Serattia marcescens	3	1	2	2	4	3	1	1	17
E. coli	2	4	3	1	4	0	1	1	16
Streptococci	0	0	0	0	3	1	1	3	8
Pseudomonas	1	2	2	2	0	0	0	2	9
Klebsiella	1	2	2	1	1	0	1	1	9
Haemophilus	0	1	0	0	4	1	0	0	6
Proteus	1	2	0	0	2	0	0	0	5
Acinetobacter	0	1	0	0	1	0	0	0	2
Citrobacter	0	0	0	1	0	0	0	0	1
Candida	0	1	1	0	0	0	0	1	3
Bacillus sp.	0	0	0	0	0	1	0	0	1
Corynebacterium	1	1	1	0	0	0	0	0	3
Morganella morganii	0	0	0	0	0	0	1	0	1

[a] CFZ, cefazolin; CFX, cefuroxime; CRO, ceftriaxone; A-N = amoxicillin + netilmicin.

most likely pathogens but need not to include drugs active against every potential pathogen. Regimens that decrease the total number of exogenous or endogenous infecting organisms permit host defenses to resist clinical infection [16]. Clinical and experimental studies have shown that antibiotics could be effective only under certain conditions. It is necessary to achieve high level concentrations in serum and tissues during the operative procedure, which is the time of maximal contamination [17,18]. When the drug is undetectable during or at the end of operation, infection is relatively common [19]. Therefore, the optimal time for administration of prophylaxis is at the induction of anesthesia [16].

In case of re-exploration, it is recommended to repeat antibiotic prophylaxis in order to achieve again adequate plasma levels during the critical period of the surgery procedure, unless a long acting drug is used. All these recommendations have been followed in the above trials. It is doubtful that postoperative infections can be entirely eliminated. Apart from the use of antibiotics, other measures must be taken in order to decrease the risk of infection. Optimizing the operating room environment, the surgical and operating room protocols and the awareness of personnel can all contribute to lowering infection rates [20].

However, the optimum duration of the antibiotic regimen has been controversial for long time. In the early period of cardiac surgery, antibiotics were administered for several days. The shortest safe period remained unclear, especially in the case of single shot prophylaxis that stayed for a long period controversial.

5. Historical background

Sutherland et al. published, in 1979, a prospective study of 693 consecutive patients showing that in elective coronary surgery no antimicrobial prophylaxis was necessary [21]. The wound infection rate was 0.8%. These results initiated a worldwide discussion.

At that time, in the Department of Surgery at the University Hospital in Zurich, cefazolin (4×0.5 g, i.v.) was applied in routine cardiac surgery for 4 days. However, this treatment was often continued for 7–10 days.

On the occasion of Sutherland's publication we searched retrospectively 500 consecutive patients and found that the postoperative infection rate in the 4-day cefazolin group was 6%, while in the 7-day group rate was 12%. It was clear that such a study had no major value, as high risk patients and those with complications were treated longer with antimicrobials. Nevertheless, it became obvious that a longer antimicrobial application was not of definite advantage.

A prospective randomized study comparing placebo with 4-days of cefazolin administration was considered too risky and most probably unethical due to the results of Fong et al. who had shown a very high infection rate in the placebo group [22]. We therefore designed and performed in 1980/81 our first prospective randomized study comparing a 4-day cefazolin (4×0.5 g/day, i.v.) administration with a 2-day cefuroxime (2×1.5 g/day, i.v.) regimen. In this study, 566 patients were enrolled: 281 in the cefazolin and 285 in the cefuroxime regimen. Neither in the 30 days total infection rate (5.7 vs. 5.3%) nor in the wound infection rate (2.5 vs. 1.1%) statistical difference could be observed, although the trend was in favor of the shorter regimen [3].

In 1982/83, the next study compared the 2-day cefuroxime regimen (2×1.5 g, i.v.) with a 2-dose ceftriaxone (2 g at the induction of anaesthesia plus 1 g 24 h later). Of the 512 patients enrolled in the study, 258 received cefuroxime and 254 ceftriaxone. Again, no difference in total (4.7%) and in wound infection rate (1.2%) was found [4].

In the meantime, in order to be sure that a single dose ceftriaxone application would be sufficient, we conducted an extensive pharmacokinetic study measuring plasma levels in the first 24 h after 2 g ceftriaxone given at the induction of anesthesia [23]. In this study, 110 patients were enrolled. The plasma levels were so high (265 μg/ml at the beginning of the operation, 103 μg/ml at the beginning of the cardiopulmonary bypass, 95 μg/ml at the end of operation, and 24 μg/ml 24 h later), that the MIC90 of bacteria like Enterococci (128 μg/ml), *Pseudomonas aeruginosa* (64 μg/ml) and *Bacteroides* (32 μg/ml) were lying under the curve [23].

Therefore, we skipped the above mentioned study and decided to compare the single dose ceftriaxone regimen to the universally used and worldwide accepted antimicrobial prophylaxis regimen with cefazolin (4×0.5 g for 1 day). Out of 883 patients, 439 received cefazolin and 444 ceftriaxone. Again, no difference in the 30 days total infection rate (5 vs. 4.5%) and the 30 days wound infection rate (0.4 vs. 1.3%) was found [5].

In order to be sure that not only the 30 days infection rate was more or less similar between the two treatment groups we continued the study up to 1049 patients and checked the 6 months infection rate [24]. The 30 days total infection rate was 5.1 vs. 5.3% and the 30 days wound infection rate was 0.8 vs. 1.9%. The 6 months total infection rate was 7.6 vs. 9.3%, again not showing any statistically significant difference between the two groups.

In 1993, one of the authors (S.G.) left the University Hospital of Zurich to work for the newly formed Onassis Cardiac Surgery Center, in Athens. Three surgical teams of the Center (trained in USA) had agreed to administer as surgical prophylaxis netilmicin (2×150 mg i.v.) and amoxicillin (3×2 g i.v.) both for 4 days. An ideal situation to compare a single dose prophylaxis to a 4-day regimen.

There had been already a background of 1000 operations with the above regimen before starting in 1994 the next study comparing a single dose cefuroxime vs. a 4-day amoxicillin/netilmicin regimen. Out of 1009 patients enrolled, 508 received amoxicillin plus netilmicin and 501 cefuroxime. Total infection rate (5.6 vs. 5.7%) and wound infection rate (0.6 vs. 1.2%) were again similar in both groups [6].

In the present study we have put together the results of the

four major studies which enable the comparison of the various regimen: 4 vs. 2 days, 2 days vs. 2 doses, 1 day vs. single dose, and at the end single dose vs. 4 days. The circle is in this way closed and the results show a unique similarity. Despite the different duration time of the antibiotic administration and the different antibiotics used (cephalosporins of the first, second and third generation, plus a combination of netilmicin and amoxicillin), the total wound infection rate in our meta-analysis ($n = 2.970$ patients) was 1.1%. Range varied between 0.4 and 2.5% and trend was generally in favor of the shorter regimen! Sepsis rate was 0.8% (range 0.4–1.6%); nosocomial pneumonia rate was 2.0% (range 0.7–2.9%); UTI rate was 0.4% (range 0–1.4%). Total infection rate was 5.2% (range 4.5–5.7%).

All these results were similar despite the change of patients' mean age from 53 to 60 years, the higher risk group, and the change of patients' mean weight from 68 to 77 kg.

It is interesting to note that in the first three studies the comparison was made between consecutive regimen varying from 4 days to a single dose regimen, but this comparison was not made contemporary. In contrast, in the last study the comparison of single dose versus the 4-day regimen has been made contemporary. In addition, the result of the latter study was not influenced from changes that had been made during those years regarding the perioperative conditions and operating protocols. Total infection rate has not changed during those years. This fact could mean that total infection rate could not easily diminish further by using newer cephalosporins nor by varying the antimicrobial regimen. However, things change rapidly in cardiovascular surgery. For this reason, a continuous re-evaluation of antimicrobial policy is necessary. Data from different institutions should be taken into consideration for the choice of the optimum prophylactic antimicrobial regimen. Local resistance problems with MRSA, MRSCN or vancomycin resistant Enterococci may need other more potent regimen.

6. Conclusions

The 'meta-analysis' of these four studies, which compared seven different regimen since 1980, showed no statistically significant difference in the frequency of postoperative infectious complications. If a cephalosporin is administered properly at the induction of anesthesia, a low infection rate occurs that can not be lowered further by longer duration of antimicrobial administration. A single dose prophylaxis of 2 g ceftriaxone (i.v.) or 3 g cefuroxime (i.v.) is safe, cheep and effective.

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