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# ANTIMICROBIAL TREATMENT EVALUATION AT NORK-MARASH MEDICAL CENTER

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## Summary

### Objectives
This paper studied the antibiotic management of hospitalized patients, at Nork-Marash Medical Center (NMMC), to evaluate alternate criteria for antimicrobial treatment.

### Methods
A retrospective cross-sectional record review of antibiotic use included 60 patients hospitalized from November 2003 to June 2004. Inclusion criteria were hospitalization and presence of infection detected by the laboratory culture test results. The quality of antimicrobial therapy at NMMC was measured by in-depth review of medical records. The sample size was calculated according to the one sample proportion formula (hypothesized proportion 0.74 and difference 17%).

### Results
Antibiotics used for prophylaxis were consistent with the guidelines. However, the routine postoperative doses of prophylactic treatment used for NMMC patients during ICU stay were inconsistent with the guidelines.
Antimicrobial treatment was indicated in 93.3 % of patients. The pathogen was susceptible to the prescribed antibiotics in 69.8 % cases. The susceptibility rates were found to be similar at NMMC and German and Netherlands clinics ($p>0.05$). Antimicrobial treatment was judged as appropriate in 66.0 %, and the dosing regimen (dose, interval, duration) found to be appropriate in the virtually all (94.6 %) cases.

### Conclusions
The practice of giving prophylactic doses of antibiotics following surgery should be reassessed. Overall, the susceptibility of colonized pathogens to empirical antimicrobial treatment at NMMC was found similar to the rates in German and Netherlands clinics. The revealed gap between pathogen susceptibility and prescribed treatment at NMMC was mainly conditioned by the facts that antimicrobial treatment was started in uncertainty of causative agent and its susceptibility and thus clinicians relied more on clinical symptoms rather then on susceptibility test results. These reasons are presented also by antimicrobial audits in other hospitals abroad.

# 1. Introduction

## 1.1 Background

Antimicrobial therapy is distinct from other types of pharmacological treatment (1). It is based upon interrelationship between the individual patient, the drug, and the characteristics of the agent (1). Healthcare organizations are increasingly responsible for improving quality of care, defined by Donabedian as "the extent to which care provided is expected to achieve the most favorable balance of risk and benefit" (2). In the context of infection control, health care institutions assume responsibility for optimizing therapeutic outcomes in individual patients as well as establishing strategies for minimizing the development of resistant strains of microorganisms (2).

Hospital acquired infection, defined as an infection neither present nor incubating on admission to hospital, i. e. a complication due to hospital stay, is a serious problem (3). Each year, millions of patients acquire infection as a result of receiving health care in a hospital (3). Moreover, these hospital-acquired infections are often main causes of extended hospital stays that impair patient quality of life and may result in permanent disability or death (3). Patients undergoing cardiac surgery appear to be at increased risk for developing hospital acquired infections (nosocomial infections) due to presence of multiple surgical wounds (chest and lower extremity incisions), frequent postoperative utilization of invasive devices (e.g., intra-aortic balloon counterpulsation, pulmonary artery catheter), and common use of prophylactic or empiric antibiotics in perioperative period (4). Other host characteristics are risk factors for development of infection: age, immune status, physical well-being, psychological well-being, hygiene, underlying or chronic disease, other infection, medical intervention (3). Hospital acquired infections reflect the quality of services provided (3). Health care institutions are responsible for developing policies and procedures that address nosocomial infections.

To prevent and treat nosocomial and other infections, the health care community uses broad spectrum antibiotics (5). Misuse/overuse of antibiotics is costly and may result in antibiotic resistance and prolonged hospitalization (1, 2, 5). Antimicrobial resistance is a growing concern among health care professionals worldwide. Rates of antibiotic resistance are increasing in all hospitals (6). The prevalence of antibiotic resistance in any population is related to the proportion of the population receiving antibiotics and total antibiotic exposure (6). The development of antibiotic-resistant infections has been associated with significantly greater hospital mortality rates compared to similar infections caused by antibiotic-sensitive pathogens (4). Evidence suggests that health care organizations that have active antibiotic control programs can reduce the development of antimicrobial resistance (2).

Antibiotic prophylaxis is generally indicated for patients undergoing cardiovascular surgery (open heart surgery, reconstruction of abdominal aorta, procedures on leg which involve a groin incision, any vascular procedure with insertion of a prosthesis / foreign body) (6,7). The chosen antibiotics must be active against the most common expected pathological agents (7). Prophylaxis should be started preoperatively in most circumstances, ideally within 30 minutes of the induction of anaesthesia (6, 7). In all operations, administration of additional doses of antibiotics in post-surgical period does not provide any additional prophylactic benefit (6). Prophylaxis is highly likely to reduce major morbidity and hospital costs and may decrease overall consumption of antibiotics (6).

The main objective of this study was to describe and evaluate the patterns of documented use of antibiotics for in-hospital patients who developed infection at Nork Marash Medical Center.

### 1.2 Study goal and objectives

The aim of the study was to evaluate antimicrobial therapy at NMMC based on evidence-based treatment guidelines.

The study objectives were to evaluate the following criteria of antimicrobial treatment: indications for antimicrobial therapy, consistency of the prescribed therapy with susceptibility of pathogens, appropriateness of prescription and dosing regimen (dose, duration, interval) of antibiotics.

### 1.3 Quality indicators of antimicrobial drug use

The goal of antimicrobial therapy is to extinguish the infectious organism and improve an individual patient's clinical outcome. The health and well being of the patient are the paramount of the antimicrobial therapy. Quality of antimicrobial drug use is dependent on many infectious disease parameters. Pharmacokinetics and pharmacodynamics of antibiotic agent, virulence of the microorganism, and the characteristic of the individual patient are major factors need to be considered when evaluating antimicrobial therapy (2). Traditionally, optimal antimicrobial therapy is defined as maximal efficacy with minimum toxicity (1). Nevertheless, use of antimicrobials can promote antimicrobial resistance. Optimal antimicrobial therapy must consider also taking necessary measurements to prevent the emergence of resistance (1).

Evaluating the quality of antimicrobial management cannot be performed if insufficient information on the treatment is available (1). The absence or presence of reasons of antimicrobial use in the records are linked with quality of care (1). According to Maki, the appropriateness of therapy correlates with the comprehensiveness of the physician's note in the medical records diagnoses (1).

Antibiotics are generally indicated for treatment of bacterial infections (5). One of the problems with antimicrobial therapy is that it is almost always started in the uncertainty of the causative pathogen or of its susceptibility. Blind empirical therapy often consists of high-dose, broad-spectrum drugs or a combination of drugs. A rational choice of antibiotic can only be expected if the prescriber is aware of the most likely infective agent and its prevailing susceptibility patterns (1). Several audits reports mismatches of suceptibility of colonized microorganisms to empirical therapy (1). The antimicrobial therapy matched the antibiotic susceptibility patterns of the identified pathogens in 74% of the cases in German intensive care unit and in 67 % of cases in University clinic at the Netherlands (8, 9).

The clinician prescribing antibiotic treatment should have adequate knowledge of the pharmacokinetics and pharmakodynamics of prescribed antibiotics. The dose of an antibiotic should attain optimal serum concentration level to effectively combat the specific infection (1). Optimal dose interval is dependent of the half-life and the action mechanism of the drug (1). There is a shortage of evidence-based data on optimal duration of antibiotics therapy for most infectious diseases (1). Often the minimum required duration is unknown (1).

Frequency of changing prescribed antibiotics is also an indicator of the quality of antibiotic management (2). Unjustified change of antimicrobial treatment could lead to antimicrobial resistance and indicates flaws in antimicrobial management (2).

The similarity between infectious disease committee's empiric treatment and implemented antimicrobial treatment plan is a marker for the quality of antimicrobial management at NMMC.

In evaluating the quality of the antimicrobial therapy, host factors need to be considered in detail. Factors such as age, allergy or history of adverse drug reaction, renal and hepatic function can play a huge role in preventing potential medication-related problems. Some antibiotics have very severe toxic effects and should be avoided in certain conditions (5).

### 1.4 Antimicrobial drug usage at Nork Marash Medical Center

Antimicrobial therapy at NMMC is mainly initiated to prevent nosocomial infections and to treat existing infections. There is a Nosocomial Infection Control Committee at NMMC. The Committee consists of 4 members: epidemiologist, 2 surgeons (a leading and a junior surgeon), and an epidemiological nurse. NMMC Infection Control Committee directs infection control activities. The activities are determined based on the monthly statistics of cultures and their sensitivities. The general practice at NMMC is that all patients undergoing surgical treatment are initiated with perioperative prophylactic antimicrobial therapy in the operating room. After surgery, patients continue receiving prophylactic antimicrobial therapy in the Intensive Care Unit (ICU) until their discharge to wards. The choice of prophylactic antibiotic is based upon monthly statistics of pathogens and their antimicrobial susceptibility. If an infection is suspected, tissue samples are taken from patients and cultured for serology and antimicrobial susceptibility tests. Determination of the etiological agent depends not only on laboratory results but also clinical symptoms. Antibiotic prescription is often initiated based on the clinical diagnosis (empirical therapy). Once the bacteriology report (susceptibility data) is available, the antimicrobial treatment plan may be substituted with more appropriate antibiotic treatment plan. However, sometimes bacteriology report is not considered as a primary source of decision, because bacterial isolates from culture specimens may represent normal flora, colonizers, or contaminants, rather than true pathogens (5).

## 2. Methods

A retrospective cross-sectional record review study of antibiotic use was conducted at NMMC. Quality of antimicrobial therapy was measured by reviewing medical records of 60 hospitalized patients who developed infections. The sample size was calculated according to the one sample proportion formula (hypothesized proportion of susceptibility match to empirical therapy of 0.74 and difference 17%).

The inclusion criteria were hospitalization and presence of infection detected by laboratory culture test results. Patients with staphylococcus epidermidis incubated in cultures taken from surgical wounds or central catheter tips of patients whom no antibiotics were prescribed except antibiotics prescribed for prophylaxis after heart surgery were excluded from the study: according to the Infection Control Committee, the presence of staphylococcus

epidermidis in the wound or catheter alone is not an infection. A sequential list of all hospitalized patients with infection treated from November 2003 to June 2004 at NMMC was abstracted from the microbiology computerized database. An attempt was made to retrieve the patient records of the last 60 patients included in the list. As some of the records were not found in the archive, these were replaced sequentially with other patients from the list until the sample size of 60 was reached.

An in-depth review of the records was performed by American University of Armenia NMMC collaborative project coordinator and clinical pharmacologist. Patient demographics, health status (hepatic, renal function), antibiotics prescribed in ICU and wards (duration, dosage, interval, route of administration), allergy history, lab cultures (site of cultures, dates), culture test results (serology, antimicrobial susceptibility), and patient status at discharge were collected for each patient (Appendix 1). Based on the acquired data and clinical guidelines, pharmacologist researcher evaluated criteria on antibiotic use (10 - 14).

The quality of antimicrobial drug therapy was evaluated using a modified list of criteria defined by Gyssens (1) (Table 1).

**Table 1. Criteria for evaluation of quality of antimicrobial drug use**

| Criteria | yes | no |
|---|---|---|
| Sufficient data in the records for evaluation (all parameters present?) | | |
| Indication for antibiotic therapy? (is an antibiotic indicated or not ? ) | | |
| Efficacy (susceptibility, antimicrobial activity) | | |
| Appropriate choice of antibiotic (is antibiotic susceptible and is it a good choice)* | | |
| Toxicity, allergic reactions | | |
| Appropriate dosing regimen (duration, dose, interval)* | | |
| Times antibiotic changed | | |

* Marked criteria were evaluated also as "not treated"

Antimicrobial therapy was evaluated as "appropriate", "inappropriate", "not treated" or "insufficient data". Antibiotic choice was evaluated as appropriate if the culture was susceptible to the prescribed antibiotics (all pathogens cultivated were susceptible to prescribed antibiotics), and the choice of antibiotics was appropriate in terms of susceptibility scale (1+ to 4+) and infection location. When these criteria (at least one) was not met, the therapy was evaluated as "inappropriate". Cases with positive lab results and no antimicrobial treatment (except the antibiotic prescribed for prophylaxis) were judged as "not treated". The cases where there was missing data (no sheets for drug prescription, no data on infection susceptibility), were judged as "insufficient data".

**Data analysis**

The data was entered and analyzed using SPSS 11.0 statistical package.

## 3. Results

*Demographic characteristics*

Records of 60 infected patients were reviewed. Of them, 41 were male, 19 female; 46 were adults, 14 children; 18 (30.0 %) patients were from Yerevan, 23 (38.7 %) from regions, 19 (31.7 %) from abroad. The proportion of patients from abroad in the studied sample of infected patients was significantly higher than the proportion of this category of patients among all hospitalized during 2004 (31.7% vs. 14.0 %, p=0.0001), indicating that patients from abroad developed infections more frequently than those from Armenia.

With few exceptions, the patients were postsurgical patients. Of the sample, 33 (55.0 %) were diagnosed with ischemic heart disease, 16 (26.7 %) with congenital heart disease, and 11 (18.3 %) with acquired heart disease. Out of 60 patients, 29 (48.3 %) had no comorbidities, while 21 had diabetes (38.6 %); few patients hepatic dysfunctions, renal insufficiency, or other problems. Of the sample, 10.0 % reported a history of allergy.

Body Mass Index (BMI) was calculated for all adult patients. They were divided into four BMI categories (3). As shown in Table 2, 77.5 % of patients were overweight.

**Table 2. BMI category distribution of the sample**

| | Frequency | Valid Percent (%) |
|---|---|---|
| underweight | 1 | 2.5 |
| normal | 8 | 20.0 |
| overweight | 10 | 25.0 |
| obese | 21 | 52.5 |
| **Total** | **40*** | **100.0** |

* Data on the remaining 20 patients was missing

*General results*

The mean ICU length of stay for patients who developed infection was 8.3 days (sd=9.5). The ICU length of stay for the non-complicated patients without infection is 2 days at NMMC, which is significantly shorter as compared to the stay of patients with infections (p<0.000). Thus, patients with infection stay in ICU 6.3 days longer on average. The mean length of total stay in NMMC for these patients was 24.7 days (sd=18.0).

The patients had 97 pathogens cultivated from their samples. On average, each infected had 1.6 pathogens (sd=1.0) incubated from their samples. Out of 57 patients whose temperature records were available, 54 (93 %) had fever (axillary temperature >37.2°C) (15).

Of 97 positive cultures taken from the sample, the most frequently cultivated infection was staphylococcus aureus (35), followed by staphylococcus epidermidis (18), candida (14), e.coli (12), proteus (5), klebsiella (4), arizona (3), streptococcus pneumonia (3), pseudomonas aeroginosa (2), and enterococcus (1).

The cultivated infection was different for samples taken from different sites. Staph. aureus and staph. epidermidis were mainly incubated in samples taken from surgical wounds, while e.coli and proteus from central catheter tip, candida from sputum/throat (Table 3).

**Table 3. Pathogens incubated from different sites (number/%)**

| | SA | SE | PV | KL | EC | CAN | AR | PA | STR | EN |
|---|---|---|---|---|---|---|---|---|---|---|
| **surgical wound** | 10 /30.3% | 7 /38.9% | - | - | 1 /8.3% | - | - | - | - | - |
| **sputum** | 3 /9.1% | 1 /5.6% | - | 3 /75.0% | 3 /25.0% | 5 /38.5% | 1 /33.3% | 1 /50% | 1 /100% | - |
| **throat** | 4 /12.1% | 2 /11.1% | - | 1 /25.0% | 3 /25.0% | 6 /46.2% | - | - | - | - |
| **central catheter tip** | 9 /27.3% | 5 /27.8% | 4 /80.0% | - | 4 /33.3% | 1 /7.7% | 2 /66.7% | - | - | - |
| **aortic valve** | 1 /3.0% | 1 /5.6% | - | - | - | - | - | - | - | - |
| **peritoneal solution** | - | - | - | | - | - | - | 1/50% | - | - |
| **blood** | 3 /9.1% | 2 /11.1% | - | - | - | - | - | - | - | - |
| **urine** | 1 /3.0% | - | 1 /20.0% | - | 1 /8.3% | - | - | - | - | 1 /100% |
| **pleural fluid** | 1 /3.0% | - | - | - | - | 1 /7.7% | - | - | - | - |
| **eye** | 1 /3.0% | - | - | - | - | - | - | - | - | - |
| **Total** | 33 /100% | 18 /100% | 5 /100% | 4 /100% | 12 /100% | 13 /100% | 3 /100% | 2 /100% | 1 /100% | 1 /100% |

SA – staphylococcus aureus, SE-staphylococcus epidermidis, EC-e.coli, AR-arizona, KL-klebsiella, CAN – candida, PV – proteus vulgaris, STR – streptococcus, PA – pseudomonas aeroginosa, EN-enterococcus
* For 5 infections there was no record on the place where sample was taken

The site of infection was recorded very poorly in the microbiology database and almost not recorded in the patient records. According to the database and patient records, 10 (16.4%) patients had sternal infection, 1 leg infection, 2 superinfection, and 48 (78.7 %) had no data about the site of infection. The only way to make an inference of the possible site of infection was reviewing the sites, where from the culture samples were taken (Table 4).

**Table 4. Sites of cultures, where pathogens were incubated**

| | Frequency | Valid Percent |
|---|---|---|
| surgical wound | 18 | 19.6 |
| sputum | 18 | 19.6 |
| throat | 16 | 17.4 |
| central catheter tip | 25 | 27.2 |
| aortic valve | 2 | 2.2 |
| peritoneal solution | 1 | 1.1 |
| blood | 5 | 5.4 |
| urine | 4 | 4.3 |
| pleural fluid | 2 | 2.2 |
| eye | 1 | 1.1 |
| **Total** | **92** | **100.0** |

* For the remaining 5 positive cultures, there was no data on the site where from the samples were taken.

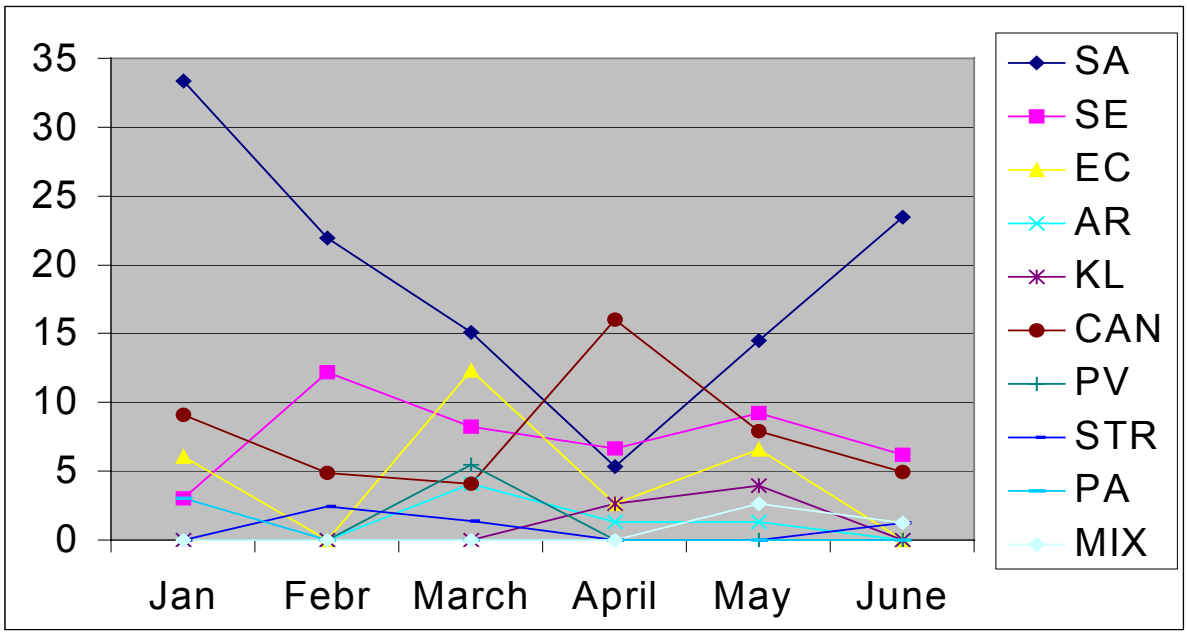
The most frequently prescribed antibiotic for prophylaxis was zinacef (84.2 %) (Table 5).

**Table 5. Antibiotics prescribed for prophylaxis**

| | Frequency | Valid Percent |
|---|---|---|
| zinacef | 48 | 84.2 |
| cipro | 8 | 14.0 |
| amoxicillin | 1 | 1.8 |
| **Total** | **57** | **100.0** |

According to the microbiology database, staph aureus, staph. epidermidis, e.coli were the most frequently encountered hospital acquired infections at NMMC during January-June 2004.

**Figure 1. Patterns of pathogens at NMMC during January – June 2004 (microbiology database)**




SA – staphylococcus aureus, SE-staphylococcus epidermidis, EC-e.coli, AR-arizona, CL-Klebsiella, CAN – candida, PV – proteus vulgaris, STR – streptococcus, PA – pseudomonas aeroginosa, MIX – mix infection

According to the NMMC institution's local susceptibility patterns, combined with the knowledge of the most likely offending organisms, a 2nd generation cephalosporin zinacef and Cipro a fluoroquinoline are rational selections for prophylactic antimicrobial regiments.

**Table 6. Sensitivity test results (% of +3, +4) for pathogens incubated in Jan-May 2004**

| | SA | | SE | | EC | | PA | | PV | | KL | | AR | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | +3 | +4 | +3 | +4 | +3 | +4 | +3 | +4 | +3 | +4 | +3 | +4 | +3 | +4 |
| zinacef | 30 | 23 | 18 | 9 | 6 | 6 | 0 | 0 | 75 | 0 | 0 | 20 | 25 | 0 |
| ceftazidime | - | - | 5 | 5 | 22 | 0 | 0 | 0 | 100 | 0 | 80 | 0 | 50 | 0 |
| cipro | 14 | 61 | 32 | 32 | 11 | 44 | 0 | 0 | 25 | 75 | 0 | 100 | 25 | 75 |

| | SA | | SE | | EC | | PA | | PV | | KL | | AR | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | +3 | +4 | +3 | +4 | +3 | +4 | +3 | +4 | +3 | +4 | +3 | +4 | +3 | +4 |
| ceftriaxone | 30 | 14 | 23 | 0 | 56 | 17 | 0 | 0 | 0 | 50 | 60 | 20 | 25 | 0 |
| gentamicin | - | - | - | - | 28 | 0 | 0 | 0 | 50 | 0 | 40 | 0 | 50 | 0 |
| vancomycin | 11 | 2 | 9 | 0 | - | - | - | - | - | - | - | - | - | - |
| erythromycin | 25 | 16 | 14 | 0 | - | - | - | - | - | - | - | - | - | - |
| clindamycin | 14 | 48 | 14 | 27 | - | - | - | - | - | - | - | - | - | - |
| cloxacillin | 16 | 48 | 14 | 18 | - | - | - | - | - | - | - | - | - | - |
| emipenem | - | - | - | - | 78 | 17 | 100 | 0 | 75 | 0 | 40 | 20 | 100 | 0 |
| lyncomicin | 7 | 48 | 5 | 36 | - | - | - | - | - | - | - | - | - | - |
| ofloxacillin | 18 | 23 | 9 | 0 | 6 | 6 | 100 | 0 | 50 | 25 | 20 | 0 | 50 | 0 |
| cefazoline | 27 | 18 | 18 | 5 | - | - | - | - | - | - | - | - | - | - |
| augmentin | 16 | 9 | 14 | 9 | 39 | 0 | 50 | 0 | 50 | 0 | 20 | 0 | 50 | 0 |
| doxycycline | 25 | 20 | 9 | 0 | - | - | - | - | - | - | - | - | - | - |
| pos.samples | 100 (44) | | 100 (22) | | 100 (18) | | 100 (1) | | 100 (4) | | 100 (5) | | 100 (4) | |

SA – staphylococcus aureus, SE-staphylococcus epidermidis, EC-e.coli, PA – pseudomonas aeroginosa, PV – proteus vulgaris, CL-clebsiella, AR-arizona

Of 149 antimicrobial courses, a total of 122 courses of different antibioticotherapies (excluding antifungals prescribed and the repeated courses of the same antibiotic) were prescribed to 58 patients with bacterial infection for prophylactic or treatment purposes. The mean number of antibiotics was 2.1 per patient (sd=1.0).

Of 74 antimicrobial treatment courses (excluding antifungals and antibiotics prescribed for prophylactic purposes) prescribed for treatment purposes only, the most frequently used antibiotic was ciprofloxacin 43 (58.1 %), followed by tienam 6 (8.1 %) and zinacef 6 (8.1 %), then ampicillin 4 (5.4 %), augmentin 3 (4.1 %), lyncomicin 3 (4.1 %), vancomycin 2 (2.7%) and others (netromicin, amikacin, fortrum, clindamycin, rocefin, tetracyclin) by 1 (1.4 %). The antibiotic primarily prescribed after an diagnosed infection was ciprofloxacin (80.4 %). As a second choice, ampicillin was prescribed most frequently.

Of 58 (2 missing) patients 18 (31.0 %) were prescribed nystatin for treatment or prophylaxis of fungal infection. Of 13 patients with incubated candida, nystatin was prescribed only to 7 patients (53.8 %). The remaining 4 did not receive specific antifungal treatment. In one case where nystatin was prescribed, according to susceptibility data, the cultivated candida was not sensitive to nystatin, but was sensitive to fluconazole.

Antibacterial treatment was indicated for 56 (93.3 %) patients. For the patients with positive cultures for candida, antifungal rather than antibacterial treatment was indicated.

There was sufficient data in the records for 44 (73.3 %) patients. Of these 16 records with limited data, 7 records were lacking key information like drug prescription sheets or susceptibility tests of isolated agents. Thus, for these 7 records, it was impossible to draw any conclusion about appropriateness of the prescribed antimicrobial treatment.

The susceptibility data of infectious pathogen was acquired from microbiology database. It showed that 69.8% of the patients received antimicrobial therapy in accordance with the susceptibility of the causative microorganism (Table 7). The appropriateness of antimicrobial therapy in terms of susceptibility of pathogen to empirical therapy was similar (p=0.513) in NMMC and Germany clinic 74% (8). At the University hospital in the Netherlands only 67% of clinical isolates were susceptible to empirical therapy, which was similar to the NMMC rate (p=0.661) (9).

**Table 7. Susceptibility to the causative pathogen**

| Pathogen susceptibility | Frequency | Percent |
|---|---|---|
| yes | 37 | 69.8 |
| no | 7 | 13.2 |
| not for all pathogens | 2 | 3.8 |
| not treated | 7 | 13.2 |
| Total | 53* | 100.0 |

*Antimicrobial susceptibility data was missing for 7 patients

According to the above-mentioned criteria, antimicrobial treatment was evaluated as appropriate in 66.0 % of cases (Table 8). In two cases, the pathogen was susceptible to the chosen antimicrobial treatment, however the latter was judged as inappropriate, mainly because the pathogen susceptibility to the treatment was low (1 +) and apparently there were better choices of antimicrobial treatment. In one case of a child with incubated escherichia coli, the culture was susceptible to cipro (4+) and ampicillin (1+), and the prescribed Antimicrobial treatment (course of cipro later combined with ampicillin) was evaluated as inappropriate, because it was unclear why ampicillin (with low susceptibility) was added to the treatment, while there were several more appropriate antibiotics for the particular case.

**Table 8. Evaluation of antibiotic therapy**

| | Frequency | Percent |
|---|---|---|
| appropriate therapy | 35 | 66.0 |
| not appropriate therapy | 11 | 20.8 |
| not treated | 7 | 13.2 |
| Total | 53* | 100.0 |

* For 7 patients, there was insufficient data.

There was antibiotic change in 22 (36.7 %) patients (excluding the same antibiotics taken on and off). In 9 patients, the same antibiotic was given several times (taken on and off) during the patient stay in the center. In the case presented in Table 9, zinacef was prescribed and then taken off 4 times, ciprofloxacin 2 times, and augmentin 2 times.

**Table 9. Antibiotic treatment description of a case**

| On date | Off date | antibiotic | Dose |
|---|---|---|---|
| 16.02.04 | 18.02.04 | zinacef | 750 mg x 3 |
| 20.02.04 | 26.02.04 | ciprofloxacin | 750 mg x 2 |
| 26.02.04 | 27.02.04 | zinacef | 250 mg x 2 |
| 27.02.04 | 03.03.04 | cloxacillin | 500 mg x 4 |
| 29.02.04 | 03.03.04 | nystatin | 500000 un x 4 |

| On date | Off date | antibiotic | Dose |
|---|---|---|---|
| 03.03.04 | 04.03.04 | zinacef | 750 mg x 1 |
| 04.03.04 | 14.03.04 | ciprofloxacin | 400 mg x 3 |
| 05.03.04 | 05.04.04 | nystatin | 500000 un x 4 |
| 06.03.04 | 14.03.04 | augmentin | 2000 mg x 3 |
| 14.03.04 | 02.04.04 | zinacef | 250 mg x 2 |
| 23.03.04 | 24.03.04 | augmentin | 500 mg x 3 |

This is an example of unjustified (inconsistent with susceptibility test results) and probably excessive use of antibiotics. Such practice may result in superinfections and development of resistant strains of bacteria (2).

The duration, dose and interval of antibiotics prescription (including antifungals) were mostly appropriate. Of 147 antimicrobials (2 cases missing), the dosing regimen of 139 (94.6 %) was appropriate according to guidelines and pharmacokinetic and pharmacodynamic properties of the antimicrobial agent. In one case, vancomycin was given in 500 mg dose once in four days. Vancomycin (the drug of choice for the treatment of serious infections due to methicillin-resistant strains of Staphylococcus aureus and coagulase-negative staphylococci) display time- dependent bactericidal profile and bactericidal activity is only marginally enhanced if drug concentration exceeds the minimal inhibitory effect (MIC). Therefore, the effective dosing regiment requires drug concentration to exceed the MIC for at least 40% to 50% of the dosing interval (14). Administering the drug via continuous infusion or frequent small doses increases duration that drug concentration exceeds the MIC and appears to be correlated with good outcomes (16).

The routes of administration of antimicrobials were very poorly recorded. Hence, the data was insufficient to determine appropriateness of the tissue penetration with site of infection. Of 149 antimicrobial / antifungal therapies, the route of administration was reported only in 12.8 % (19) of cases. The reported cases indicated mainly IV route of administration (12 of 19).

The frequency of Cipro contraindicated antibiotic as a first line therapy was very high in children. Cipro is currently not recommended in children less than 18 years of age. Studies has shown that Cipro has ability to inhibit DNA gyrase in bacterial cells, which may be similar to topoisomerases in mammalian cells contributing to arthropathy with erosions of the cartilage in weight bearing joints of immature animals; green discoloration of teeth in newborns has been reported; Achilles tendonitis and tendon rupture have been reported with fluoroquinolones; prolonged use may result in superinfection; central nervous system stimulation may occur resulting in tremors, restlessness, confusion, and very rarely hallucinations or convulsive seizures. Thus currently quinolones may be indicated if first-line antibiotics have failed and the child and/or infant are in a life-threatening infection that is otherwise untreatable. (17, 18, 19) (Table 10).

**Table 10. Contraindications reported to the prescribed antibiotics by age**

| | pediatric | | adult | |
|---|---|---|---|---|
| **Contraindications** | **Count** | **%** | **Count** | **%** |
| no | 4 | 9.1% | 40 | 90.9% |
| yes | 10 | 90.9% | 1 | 9.1% |

No adverse drug reactions or allergies to the prescribed antibiotics were reported in patient records.

Of 60 patients, 54 (93.3 %) were discharged with recorded clinical improvement and 4 (6.7%) patients died. The number of pathogens incubated from different sites of patients discharged with improvement was 1.5 (sd=0.9), for patients who died 3.8 (sd=0.5). The difference in the numbers of incubated pathogens was statistically significant ($p<0.0001$). For 2 patients, death was a result of superinfection. Multi-resistant strains of bacteria were incubated in those patients. The mean number of prescribed antibiotics was 3.3 (sd=2.1) for patients who died and 2.1 (sd= 1.0) for patients with clinical improvement. The difference here was statistically insignificant.

## 4. Limitations

Limitations of the study were mainly due to the shortcomings of data recording at NMMC. Recording flaws were observed in both sources used during the study: microbiology database and patient records. This resulted in high percentages of missing data. Another limitation was that the underlying logic of antibiotic treatment was nowhere described.

Due to difficulties in locating records in the archive, it was impossible to generate the needed retrospective data for the initially selected sample, and new cases were added to maintain the sample size, possibly biasing the sample.

Judgment about the presence of infection was mostly made based on bacteriology reports, while the specific clinical symptoms of patients should also be considered. But, as the information in records was limited, it was difficult to acquire complete picture of clinical symptoms of patients. Only some of the symptoms like fever and, in some cases, white blood cells count, were considered. While trying to assess ambiguous cases, attempts were made to collect lacking information from the staff involved in treating particular patients. However, this tactic was not productive because of recall.

## 5. Discussion

According to the data, about one-third (31.7 %) of infected patients were from abroad, which is significantly higher than the overall proportion of patients from abroad. Referral of more complex cases from abroad as compared to the locals could be one of the possible reasons for this finding. It is possible also that there was lack of natural immunity in patients from abroad to local strains. Among infected, the proportion of those with different comorbidities was also rather high. Three-fourths of patients who developed infections, according to their BMI, were overweight. The latter two characteristics, thus, could be possible risk factors for developing infection in post-surgical period.

The length of stay (both the ICU length of stay and the total hospital stay) was significantly longer for patients with infection as compared with uncomplicated patients. This finding was consistent with the literature data.

The antibiotics used at NMMC for preventing post-surgical infection were appropriately chosen according to the currently used guidelines. However, the additional postoperative

doses of antibiotics used as continuation of prophylactic treatment were not supported by the guidelines. The practiced post-operative use of antibiotics for prophylactic purposes is costly and may result in pathogen resistance.

Flaws in data reporting were observed in both sources used during the current research: patient records and microbiology database. The signs of the infection were almost never described in patient records either by physicians or nurses. For the majority of reviewed cases, the discharge summaries and daily records of patient's health status in ICU or wards lacked any information about infection. Fever and initiated antimicrobial treatment (an antibiotic prescribed in addition to the one used for prophylaxis) reflected in the records were often the only signs indicating the presence of infection. Among other infrequent notes found in patient records indicating an infection, were notes pointing out that cultures where taken or a pathogen was incubated. Very rarely, a sheet was incorporated in patient record with description of culture dates, sites, and pathogens incubated.

The microbiology database mainly contained information about cultures (sites, dates) pathogens incubated, antimicrobial susceptibility, and antibiotic used for prophylaxis. The field of infection site was very poorly recorded. The infection class field was almost always blank (records in this field were found for only 3 patients out of 60). In some cases, the entered information was incomplete: pathogens incubated (mentioned in the records) were not entered in the database. Sometime there was inconsistency between the database and records (hand infection vs. foot infection). The antibiotics used for treatment were not recorded in the database.

The antimicrobial treatment plan was never explained or justified, which is really important, especially taking into account the existence of cases where numerous antibiotics were used or the same antibiotic was prescribed and then taken off several times.

The cases of contraindicated antibiotic prescription were mainly connected with prescription of ciprofloxacin to children. This antibiotic is not recommended for use in children, unless parents know or suspect that their children have been exposed to anthrax. Studies in young animals showed that ciprofloxacin might cause joint problems in children. At NMMC, however, ciprofloxacin is commonly prescribed to children.

The study showed that the prescribed antimicrobial treatment was indicated in 93.3 % cases, the causative agent was susceptible to the treatment in 69.8 % cases, the antimicrobial treatment was judged as appropriate in 66.0 % cases, and the dosing regimen (dose, interval, duration) was appropriate in 94.6 % cases. The frequency of appropriateness of antimicrobial treatment at NMMC (66.0%) was not significantly different from the hypothesized proportion ($H_0 = 75\%$, $p = 0.178$).

As mentioned above, the prescribed antibiotics were not always the best choice when taking into consideration the data on microorganism susceptibility. One reason could be that antimicrobial treatment is started in uncertainty of causative agent and its susceptibility. Another possible reason is that, sometimes, clinicians at NMMC rely more on clinical symptoms rather then on susceptibility test results. In this aspect, NMMC is not an exception. Antimicrobial treatment audits in many other institutions over the world often report high rates of susceptibility mismatches (1).

## 6. Recommendations

Based on the results of antibiotic management evaluation, the following measures were recommended:

- Reassess the use of additional doses of antibiotic for prophylaxis in post-surgical period during ICU stay;
- Adapt and use guidelines on antibiotic use;
- Reassess the use of ciprofloxacin in children;
- Consult pharmacologists as a measure to increase the appropriateness of antibiotic treatment;
- Improve infection recording in patient records, discharge summaries, and computerized databases (surgical, microbiology) through the following measures:
    - Allocate a special space in the records, where infection-related information could be noted (the time of infection onset, infection site, causative agent, susceptibility, treatment plan, dynamics of infection, outcome);
    - Describe the underlying logic of antimicrobial treatment (prescription of new antimicrobials, change in antimicrobials);
    - Record the above mentioned information in specially allocated spaces in the computerized database by the Infection Control Committee members;
- Evaluate antibiotic management at NMMC on a regular basis.

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## Appendix 1. The data collection form for evaluating antimicrobial treatment

| | | |
|---|---|---|
| history # | | |
| resident/nonresident | | |
| physician name | | |
| sex | | |
| patient age | | |
| admission date | | |
| discharge date | | |
| ICU length of stay | | |
| diagnosis | | |
| comorbities | | |
| weight | | |
| height | | |
| allergy | | |
| renal function | | |
| hepatic function | | |
| site of infection | | |
| infection type | | |
| infection type 2 | | |
| infection class | | |
| sample1 date | | |
| sample | | |
| sample 2 date | | |
| fever | | |
| antibiotic 1 | | |
| duration of antibiotic therapy | | |
| timing of the treatment | | |
| dose of antibiotic | | |
| route of administration | | |
| antibiotic 2 | | |
| dose2 | | |
| duration2 | | |
| route of administration | | |
| Sensitivity | oxacilin<br>cefazolin<br>cefuroxime<br>ceftriaxone<br>imipenem<br>cipro | oflo<br>gentamycin<br>erythromycin<br>clendamycin<br>trimetoprim<br>cefoperazone<br>augmentin |
| Prescribed med. on discharge (drug interaction) | | |
| indication for antibiotic | | |
| is the antibiotic justified? | | |
| sufficient data for evaluation | | |
| susceptibility to the causative pathogen NMMC inf disease data | | |
| clinical outcome | | |
| antibiotic change | | |
| adverse reaction | | |
| allergy to prescribed antibiotic | | |
| contraindications | | |