

**Degree Project  
Programme in medicine  
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## **Antibiotic Resistance**

**A study of antibiotics used  
in relation to guidelines and resistance patterns at  
Kannur Medical College Super Speciality Hospital  
Kannur, India**



**The Sahlgrenska Academy**

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## Table of contents

<b>Abstract</b> .....	4
<b>Background</b> .....	5
<b>Aim</b> .....	7
<b>Methods</b> .....	8
<b>Ethics</b> .....	8
<b>Results</b> .....	8
General data.....	8
Infections.....	10
Antibiotics.....	10
Antibiotics used in relation to type of infection.....	14
Microbial investigations.....	16
Resistance patterns.....	18
<b>Discussion</b> .....	20
Infections and antibiotics.....	20
Development of antibiotic resistance.....	21
Antibiotic resistance patterns.....	22
Comparison between men and women.....	23
Strengths and weaknesses.....	24
<b>Summary</b> .....	25
<b>Conclusions</b> .....	25
<b>Antibiotikaresistens</b> –användningen av antibiotika i relation till riktlinjer och resistensmönster.....	26
<b>Aknowledgements</b> .....	27
<b>References</b> .....	28
<b>Figures and tables</b> .....	32
<b>Appendices – Form</b> .....	33

## Abstract

### Background

Antibiotics are used to treat and prevent bacterial infections. Resistance to antibiotics occurs naturally, but misuse accelerates the process. India has the largest total consumption of antibiotics in the world. A high burden of infection diseases, cheap unregulated sales of antibiotics and overuse of antibiotics in the health-care sector are all factors that contribute to the problem.

### Aim

The aim of the study is to investigate how antibiotics are used at Kannur Medical College. It will look into resistance patterns and analyze if there are any differences in the treatment between men and women.

### Method

Patients were collected at Kannur Medical College, Super Speciality Hospital. Information about the patients and their antibiotic treatments were collected from medical records. Information on cultures sent for antibiotic susceptibility testing (AST), found pathogen and resistance patterns were collected at the microbiology laboratory. The nurses asked the patients if they had taken any antibiotics before getting admitted.

### Results

The most common infections were pneumonia and urinary tract infections (UTI). The antibiotics that were most frequently used were broad-spectrum penicillins (BSP), and cephalosporins. Samples for AST were sent for 57% of the patients and 21 pathogens were found. The doctors changed antibiotics after getting the result of the AST in 50% of the cases. Out of the pathogen found, 80% showed resistance patterns that would have to be reported to Folkhälsomyndigheten if they were found in Sweden. Almost all antibiotics prescribed were in accordance with the national guidelines.

### Conclusion

The main problem is that cultures are not taken in an optimal way and that they are not sent for AST as a routine. Furthermore, the results are not always used to change into narrower antibiotics and thereby limit the development of multi-resistant bacteria (MRB).

## Background

Antimicrobial resistance is growing rapidly and has become one of the greatest threats to modern medicine and global health (1). Resistance to antibiotics occurs naturally, but misuse accelerates the process. Without effective antibiotics we are looking at a future where people will die from infections that are easily cured today. Major surgery, chemotherapy and immunomodulation would be associated with much higher risk, and may become impossible to perform safely and at the scale we do today (1). Furthermore, antibiotic resistance leads to large economical losses, due to longer hospital stays, higher medical costs and increased mortality (1). Also the development of resistance to first-generation antibiotics forces doctors to prescribe costlier second-line treatments (2).

India is a developing country and it has an extensive health care system that includes public hospitals, private hospitals and specialized Ayurvedic hospitals. The standards of the hospitals varies a lot over the country and there are large differences between rural and urban areas. Health services are available to all citizens under the so called “tax-financed public system” (3). However, there are many factors that compel people to seek private care which often result in high personal costs. Also, nearly all admission to hospitals lead to high expenditures (3,4).

Infectious diseases are a large problem in India. The country is among the 5 countries in the world with the highest number of under-5 deaths from pneumonia (5). It also has the largest total consumption of antibiotics in the world at  $12.9 \times 10^9$  units (10.7 units per person) per year (6,7). The combination of poor public health, a high burden of infection diseases, rising incomes and cheap unregulated sales of antibiotics has made India the leading country in the world when it comes to antibiotic resistance (6).

Multidrug resistance (MDR) can be defined in different ways. One way of defining it is as the resistance of a microorganism to at least 2 administered antimicrobial medicines (which are structurally unrelated and have different molecular targets) despite earlier sensitivity to them (8). MDR can also be defined as the acquired resistance to at least one agent in three or more antimicrobial categories (9). In Sweden there are 4 different resistant bacteria that doctors and laboratories are legally obligated to declare to Folkhälsomyndigheten (10). The 4 bacteria are;

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Penicillin-resistant *Streptococcus pneumoniae* (PRSP)
- Vancomycin-resistant *Enterococcus* (VRE)

- Enterobacteriaceae that produce extended spectrum beta-lactamase (ESBL)

An important factor for developing multi-resistant bacteria (MRB) is the over-use of antibiotics within the health-care sector. Some doctors in India receive compensation from pharmaceutical companies for prescribing antibiotics, a fact that contributes to the problem (6). A study from 2017 where 350 doctors in teaching hospitals in South India were asked about the antibiotic prescription in their hospitals, 89% of them believed that antibiotics were overprescribed in routine clinical practice (11).

Another important factor is the antibiotic pollution into the environment. For the moment there are no regulations of discharge of antibiotic waste (6). Furthermore, the growing demand for meat for meat and poultry has resulted in an increase of antibiotic use in the animal sector, where antibiotics are used as growth promoters (6).

Between 2005 and 2015 the use of broad-spectrum penicillins (BSP) in India increased by 51%. The use of cephalosporins increased by 127% and the use of macrolides by 54%. The use of fluoroquinolones decreased by 20% (12). Carbapenems were not widely used in India in 2000, but 2010 the consumption had risen to over 10 million standard units per year (6,7).

In order to regulate the antibiotic use, the government has made national guidelines for antibiotic use in infection diseases.

According to the national guidelines, community acquired pneumonia should preferably be treated with amoxicillin orally. If i.v. antibiotics is needed, amoxicillin-clavulanate or ceftriaxone (cephalosporin) should preferably be used. Alternative antibiotics are piperacillin-tazobactam, cefoperazone-sulbactam or imipenem (carbapenem). If MRSA is a concern linezolid (oxazolidinone) should be added. If atypical pneumonia is suspected doxycycline (tetracycline) or azithromycin (macrolide) should be used (13).

For acute uncomplicated cystitis nitrofurantoin, cotrimoxazole (sulfamethoxazole + trimetoprim) or ciprofloxacin (quinolone) should be used. An alternative is cefuroxime (cephalosporin). In case of uncomplicated pyelonephritis amikacin or gentamicin (aminoglycosides) should be used. Alternative antibiotics are piperacillin-tazobactam, cefoperazone-sulbactam or ertapenem (carbapenem). In complicated pyelonephritis piperacillin-tazobactam, amikacin or cefoperazone-sulbactam should preferably be used. As an alternative imipenem or meropenem (13).

Furthermore, to limit the unregulated over-the-counter sells of broad-spectrum antibiotics, the Central Drugs Standard Control Organization has made a list that includes 24 antibiotics such as third- and fourth-generation cephalosporins, carbapenems, antituberculosis drugs and newer fluoroquinolones. From the first of March 2014, these antibiotics can no longer be bought without a doctor's prescription (6).

Reduction of antibiotic use has an effect on the resistance patterns of the bacteria. A Canadian study that was conducted between 2002 and 2011 showed that 40% of the E. coli was resistant to ciprofloxacin in 2006. After that, the drug was used more sparingly, which led to a decrease of resistance to 29% in 2011 (14).

Kannur Medical College Super Speciality Hospital (KMC) is a private hospital with 700 beds. The admitted patients can choose to pay more money to get private rooms. The patients also have to pay extra if bacterial cultures are taken, if they do a CT or MR scan etc. Because of the tax-financed system the patients that don't have a good economy can be admitted for a very low fee and thereby also get access to health-care. Another possibility for the patient is to go to the governmental hospitals where they don't charge their patients at all.

India is a country that has great inequalities between men and women. Government statistics show that women's labor participation rate fell from 29.4 percent in 2004-2005 to 22.5 percent in 2011-2012 (15). A recent study at KMC suggests that men receive antibiotics more frequently than women (16).

## Aim

The aim of the study is to investigate how antibiotics are used at Kannur Medical College and to see if the doctors follow the national guidelines concerning antibiotic use. It aims to see what antibiotics that are prescribed, to who and why. It will analyze if bacterial cultures are taken and antibiotic susceptibility testing (AST) performed. It will also investigate if the doctors use the information in order to decrease the development of resistant bacteria. It will briefly look into how the resistance patterns of the bacteria are at the hospital today. The aim is also to see if there are any differences between male and female patients regarding these factors.

## Methods

A total of 84 patients were collected at Kannur Medical College, Super Specialised Hospital between the 18<sup>th</sup> of September to the 14<sup>th</sup> of October 2017. The study included the patients that were admitted to the intensive care unit (ICU), the medical- or pediatric wards with the suspicion of a bacterial infection. To be included in the study, the patient also had to receive antibiotics. Post-operative infections were not included in the study.

Information on age, gender, comorbidities, suspected site for infection, antibiotics, doses, administration ways and change of antibiotics was collected by going through the medical records at the different wards Monday to Saturday. Date of admission, start of antibiotic treatment and date of discharge were noted, as well as any changes in the antibiotic treatment.

Information on cultures sent for antibiotic susceptibility testing (AST) was collected from files at the microbiology laboratory with the assistance of the microbiologists. Date of the cultures and culture sites were noted, as well as identified pathogens and resistance patterns.

The nurses asked the patients in the local language if they had taken any antibiotics before being admitted to the hospital.

The patients that died or moved to another hospital are not included in the calculation of the average length of stay.

Any uncertainties were discussed with the nurses or junior doctors at the wards.

## Ethics

All the results are presented so that no patients can be identified. The study was approved by the Ethical committee of KMC.

## Results

### General data

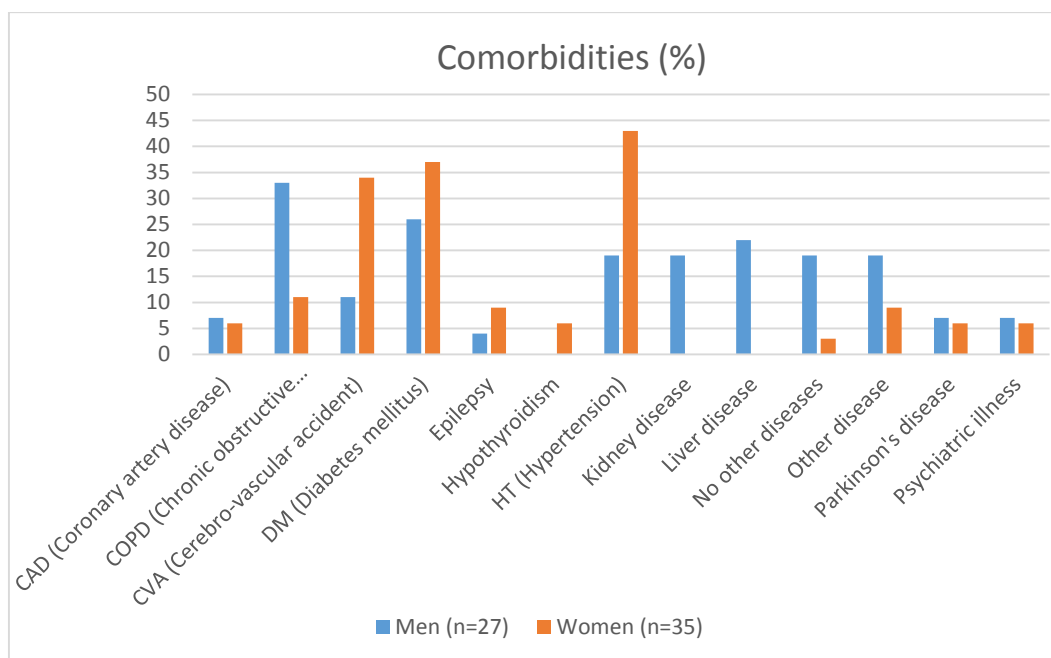
A total of 84 patients were collected for the study; 62 adults (27 men and 35 women) and 22 children (13 boys and 9 girls). In the male group the ages of the patients ranged between 42-85 years, in the female 24-92 years and in the children's group 0-9 years. The average ages were 65 years for men, 68 for women and 2 for children. In the male group 74% of the patients stayed in the general ward and 22% in private wards. In the female group 65% of the



patients stayed in the general ward and 29% in private wards. In the children's group 91% stayed in the general ward and 9% in the private wards. One man and 2 women stayed in the intensive care unit (ICU).

Length of stay in the hospital ranged between 2-15 days for men (mean 6,9 days). One patient in the group died after 2 days and one patient was transferred to another hospital after 20 days. For women the length of stay in the hospital ranged between 2-29 days (mean 8,0 days). One patient in the group died after 9 days and one was moved to another hospital after 11 days. For children the length of stay ranged between 1-8 days (average 4,5 days).

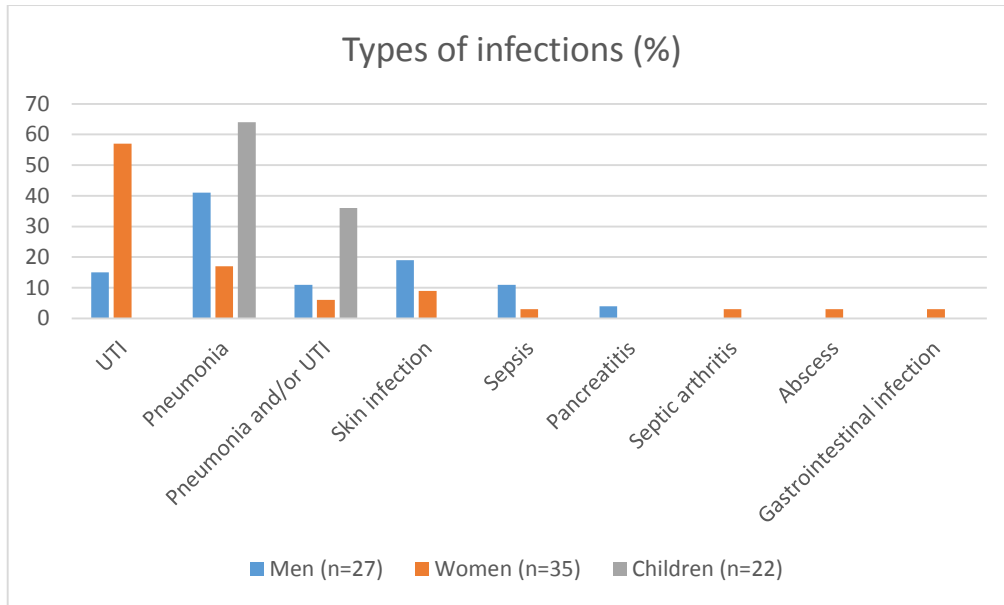
The most common comorbidities among men were chronic obstructive pulmonary disease (COPD) (33%), diabetes mellitus (26%), liver disease (22%), kidney disease or hypertension (19%), previous cerebrovascular accident (CVA) (11%). Among women the most common comorbidities were hypertension (43%), diabetes mellitus (37%), CVA (34%) and COPD (11%). There were 6 adult patients who didn't have any comorbidities (5 men and one woman). No child had any comorbidities.



**Figure 1:** Percent of patients with different comorbidities, men and women illustrated separately.

## Infections

In the male group the suspected sites for infection were pneumonia (41%), other types of infections (26%), skin infection (19%) and urine tract infection (UTI) (15%). In the female group the suspected sites for infection were UTI (57%), other types of infections (26%) and pneumonia (17%). For children the suspected sites for infection were pneumonia (64%) and pneumonia and/or UTI (36%).

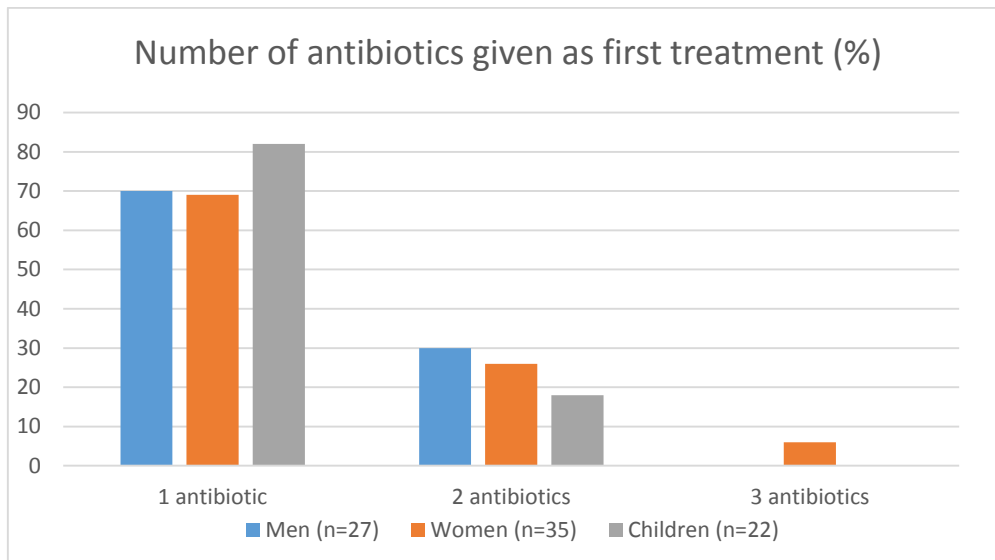


UTI=urinary tract infections

**Figure 2:** Types of infections in percent. Men, women and children illustrated separately.

## Antibiotics

Among the 84 patients admitted to the hospital with the suspicion of a bacterial infection 73% received only one antibiotic (men 70%, women 69% and children 82%) and 25% received 2 antibiotics at the same time (men 30%, women 26% and children 18%). There were 2 female patients that received 3 antibiotics at the same time.



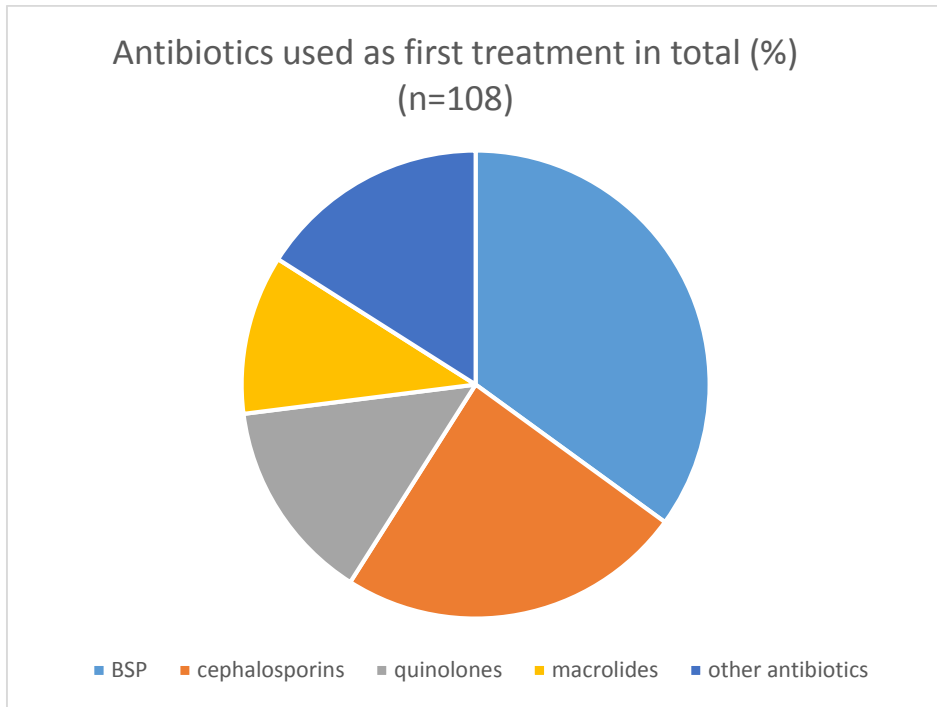
**Figure 3:** Percent of patients that received 1, 2 or 3 antibiotics. Men, women and children illustrated separately.

In total 108 antibiotics were given to the 84 patients as first treatment. The antibiotics that were most commonly used in total were;

1. broad-spectrum penicillins (BSP) 35% (men 34%, women 15%, children 73%)
2. cephalosporins 24% (men 29%, women 23%, children 19%),
3. quinolones 14% (men 20%, women 17%, children 0%)
4. macrolides 11% (men 9%, women 15%, children 8%)

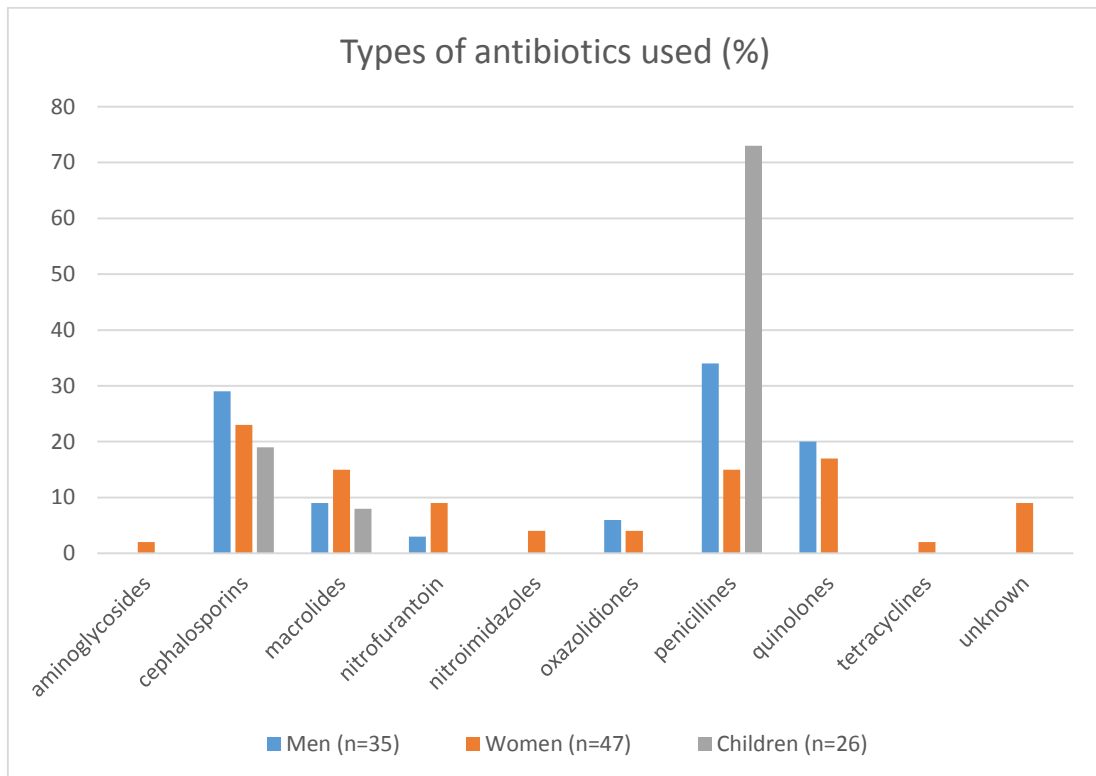
Other antibiotics were used in 16% of the cases.

If children are excluded, the most frequently used antibiotics among the adults were Cephalosporins (26%) followed by BSP (23%).



BSP= broad-spectrum penicillins

**Figure 4:** Percent of antibiotics used as first treatment divided into groups of antibiotics with similar molecular targets



**Figure 5:** Percent of types of antibiotics used as first treatment. Men, women and children illustrated separately.

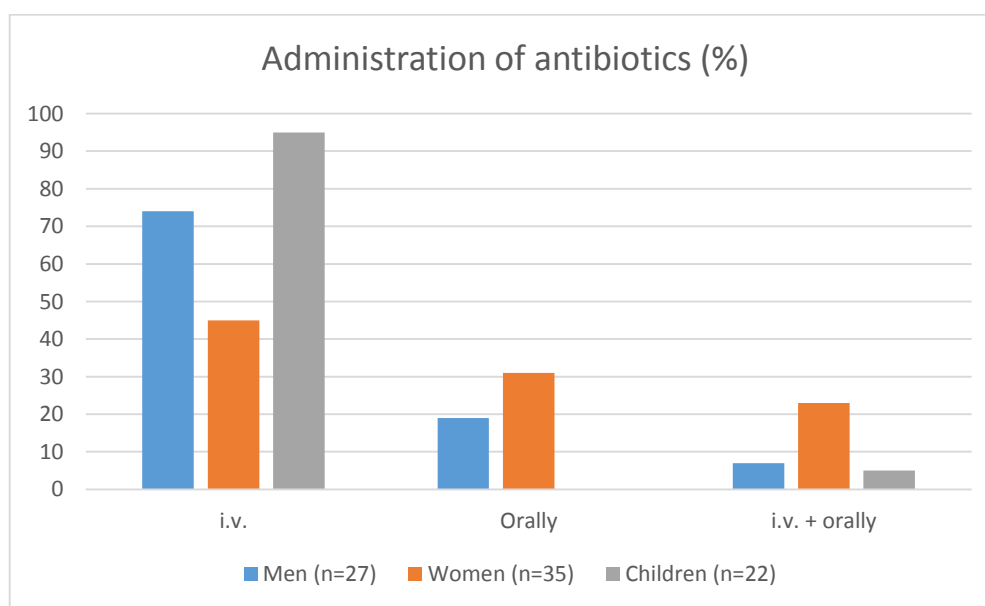
**Table 1: Types of antibiotics used**

Group of antibiotics	Men	Women	Adults	Children	Total
BSP	12	7	19	19	38
cephalosporins	10	11	21	5	26
aminoglycosides	0	1	1	0	1
tetracyclines	0	1	1	0	1
macrolides	3	7	10	2	12
oxazolidiones	2	2	4	0	4
quinolones	7	8	15	0	15
nitroimidazoles	0	2	2	0	2
nitrofurantoin	1	4	5	0	5
unknown group	0	4	4	0	4
<b>Total</b>	<b>35</b>	<b>47</b>	<b>82</b>	<b>26</b>	<b>108</b>

BSP = Broad spectrum penicillins

Intravenous antibiotics were given to 68% of the patients (men 74%, women 45%, children 95%). Oral treatment only was given to 19% (men 19%, women 31%, children 0%).

Simultaneous oral and intravenous treatment was given to 13% (men 7%, women 23%, children 5%) of the patients.

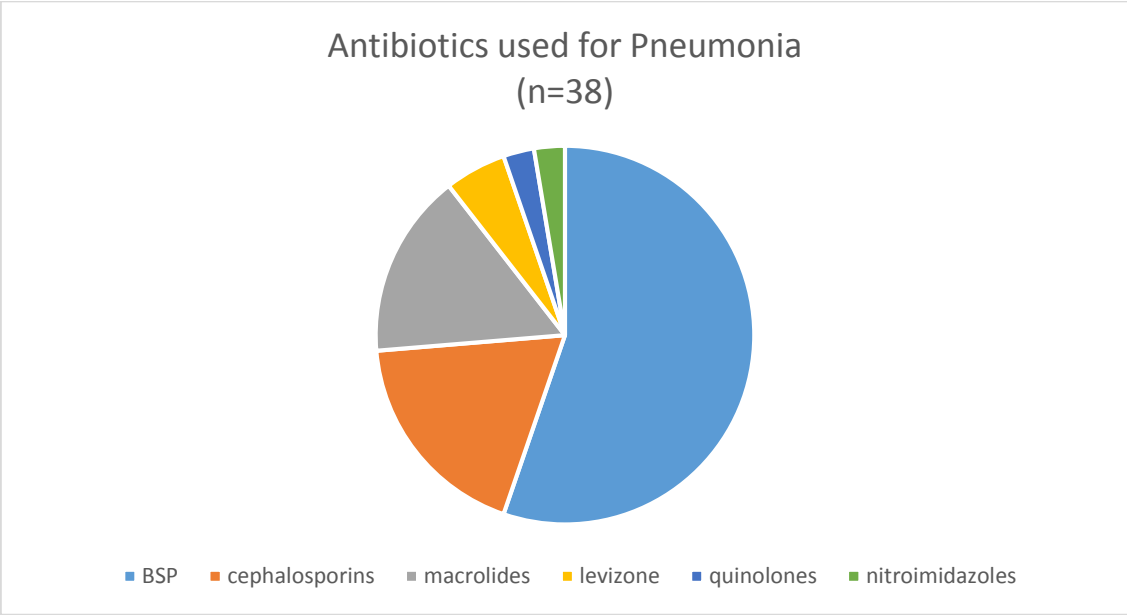


**Figure 6:** Route of administration of antibiotics in percent. Men, women and children illustrated separately.

At the question whether the patients had taken any antibiotics before being admitted to the hospital, 77% answered no (men 81%, women 86%, children 59%). All the patients that answered yes answered further that the antibiotics they had taken was prescribed by a doctor.

**Antibiotics used in relation to type of infection**

Out of the 84 patients that were admitted to the hospital with the suspicion of a bacterial infection, 31 patients were admitted with the suspicion of pneumonia (11 men, 6 women and 14 children). Most patients received single drug therapy (24 patients) and the rest received two types of antibiotics. In total 38 antibiotics were given to the patients and the most frequently used antibiotics were; BSP (21 patients), cephalosporins (7 patients), macrolides (6 patients) and other antibiotics (4 patients). Only 2 patients received antibiotics that are not recommended by the national guidelines and for 2 patients the answer is unclear. Thereby, 89-95% of the prescribed antibiotics for pneumonia were in accordance with the national guidelines.

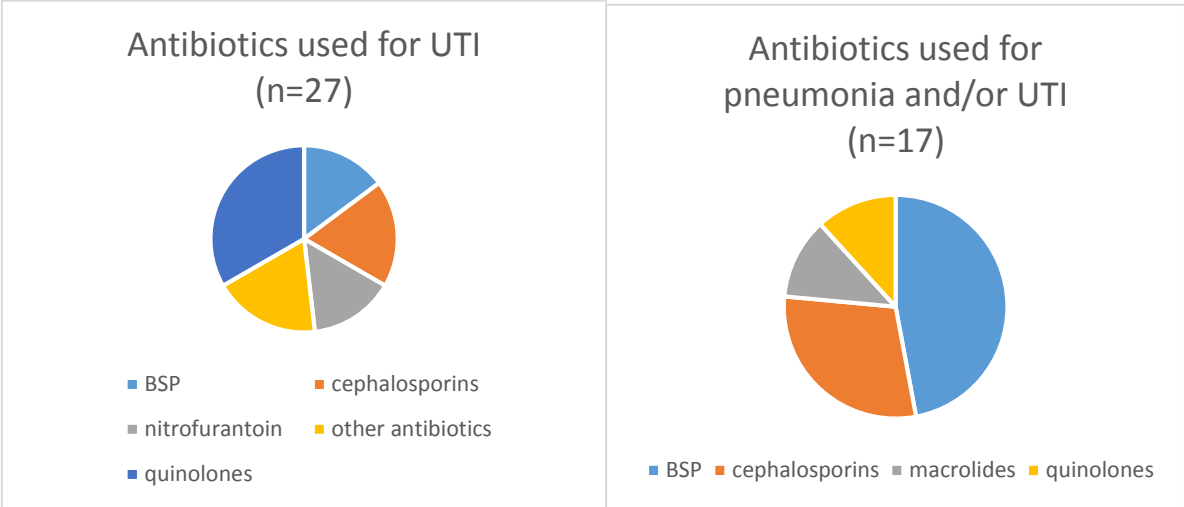


**Figure 7:** Total antibiotics used for pneumonia

Urinary tract infection (UTI) was the suspected site for infection in 24 patients of the admitted patients (4 men and 20 women). Most patients received single drug therapy (21 patients) and the rest received two types of antibiotics. The most frequently used antibiotics were quinolones (9 patients), cephalosporins (5 patients), other antibiotics (5 patients) and BSP or nitrofurantoin (4 patients each). All the patients received antibiotics according to the national

guidelines except for 2 patients that received macrolides. For 2 patients the answer is unclear. Thereby, 85-93% of the antibiotics prescribed for UTI were in accordance with the national guidelines.

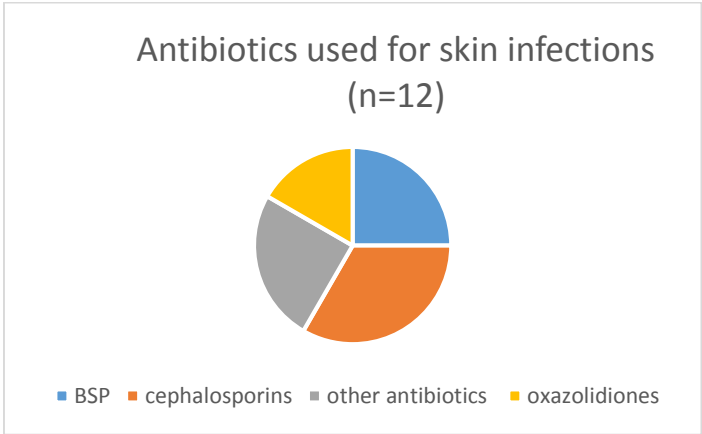
In 13 patients the doctors were not sure if the patient had pneumonia and/or UTI (3 men, 2 women and 8 children). In total 17 antibiotics were prescribed and the most frequently used were BSP (8 patients), cephalosporins (5 patients), and macrolides or quinolones (2 patients each).



BSP = broad spectrum penicillins  
 UTI = urinary tract infections

**Figure 8:** Antibiotics used in total for UTI and pneumonia and/or UTI

Skin infections were the suspected sites for infection for 8 of the patients in the study (5 men and 3 women). In total 12 antibiotics were prescribed; cephalosporins (4 patients), BSP (3 patients), other antibiotics (3 patients) and oxazolidiones (2 patients).

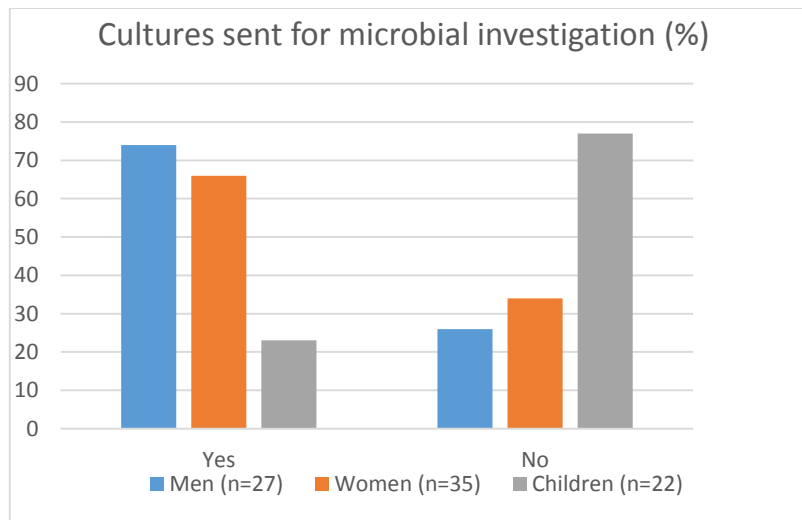


BSP= broad-spectrum penicillins

**Figure 9:** Antibiotics used in total skin infections

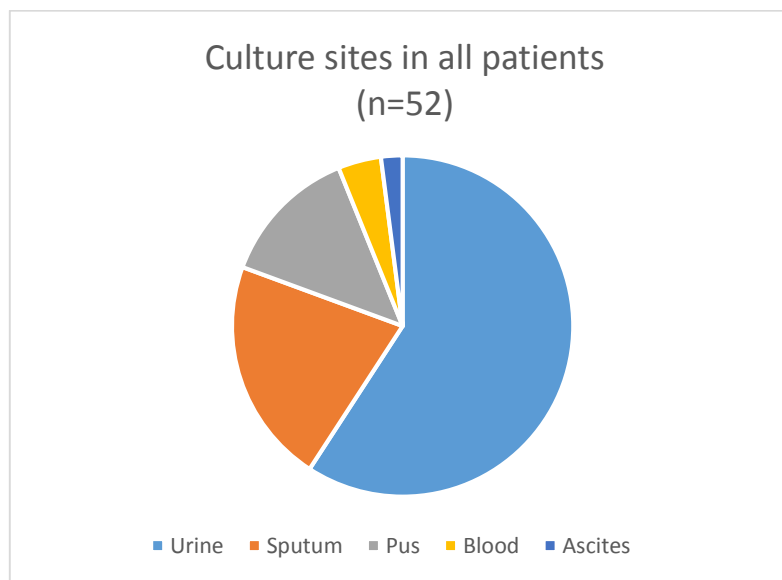
### Microbial investigations

In total 52 samples were taken from 48 patients and sent for antimicrobial susceptibility testing (AST). 21 of them were taken in the male group from 20 patients, 26 samples from 23 patients in the female group and 5 samples from 5 patients in the children's group. Thereby cultures were sent for in 57% of the patients that were included in the study (men 74%, women 66%, children 23%).



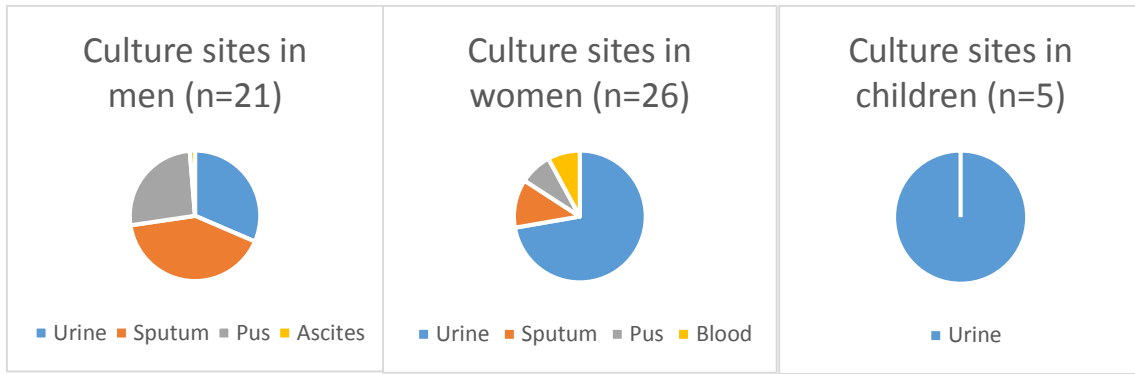
**Figure 10:** Percent of cultures taken and sent for antimicrobial susceptibility testing (AST). Men, women and children illustrated separately

Out of the 52 cultures that were taken and sent for AST, 58% of them were taken from urine, 21% from sputum and 13% from pus. Also 2 blood cultures and one ascites fluid culture were sent for AST.



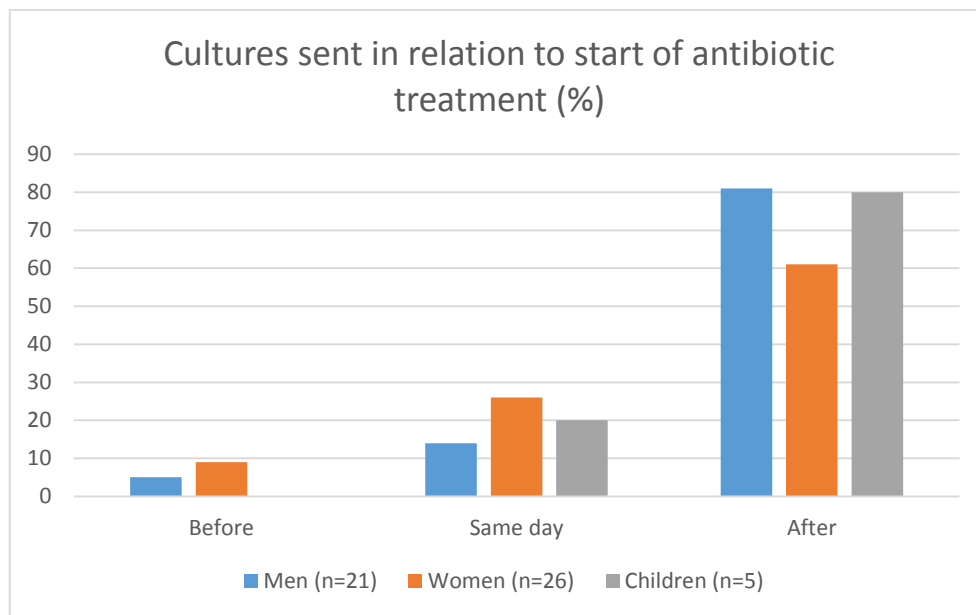
**Figure 11:** Culture sites in all patients





**Figure 12:** Culture sites illustrated separately for men, women and children.

In 3 cases (6%) the samples were sent before the treatment started. In 10 cases (19%) the samples were sent the same day as the antibiotic treatment started and in 38 cases (73%) the samples were sent at least one day after the treatment started. For one patient, the date of the culture is missing.

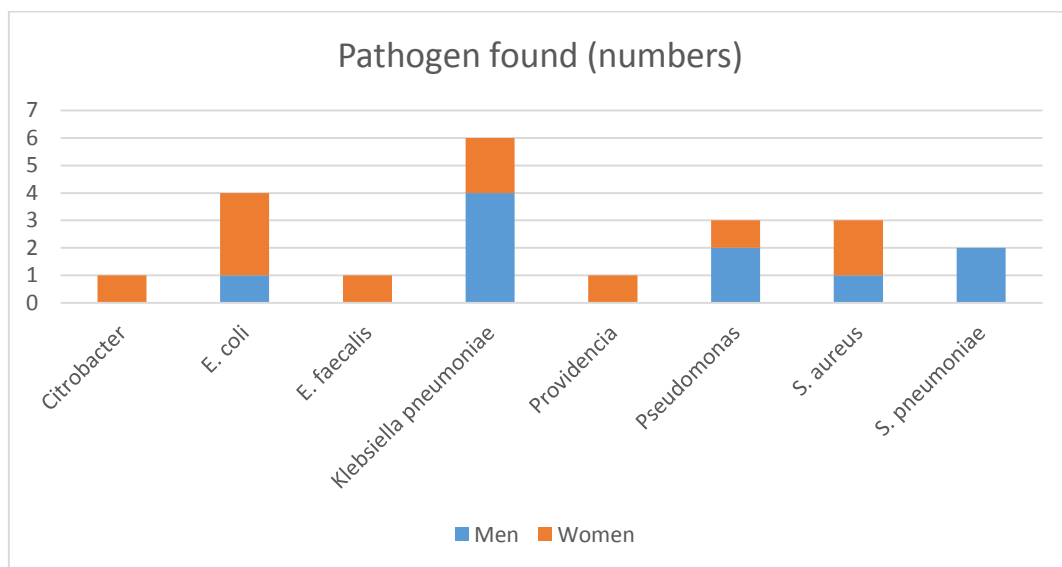


**Figure 13:** Cultures sent for in relation to start of antibiotic treatment in percent. Men, women and children illustrated separately.

Out of the 52 samples that were sent for AST, growth of pathological bacteria was seen in 20 of them (9 men and 11 women). No positive culture was found in the children. For the men, one of the positive cultures were sent for investigation the same day as the antibiotic treatment started and the rest after treatment started. For the women, one of the positive cultures were sent one day before treatment started, 4 the same day and 6 after treatment started.

The pathogen found were;

- 6 cases of *K. pneumoniae* (4 in sputum, one in pus and one in urine)
- 4 cases of *E.coli* (3 in urine and one in pus)
- 3 cases of *Pseudomonas* (2 in pus and one in urine)
- 3 cases of *S. aureus* (one in each blood, urine and pus)
- 2 cases of *S. pneumoniae* (sputum)
- 1 case of *Citrobacter* (urine)
- 1 case of *E. faecalis* (pus)
- 1 case of *Providencia* (pus)



**Figure 14:** Number of pathogen found, men and women illustrated separately

### Resistance patterns

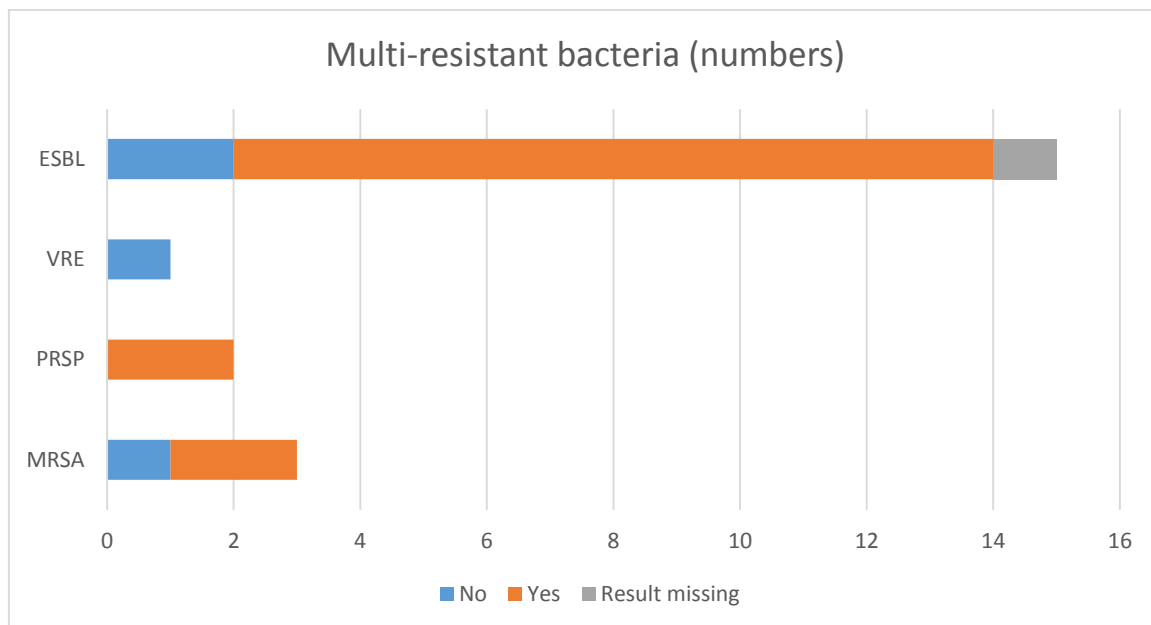
The groups of resistant bacteria that we are interested in analyzing are; MRSA, PRSP, VRE and Enterobacteriaceae that produce ESBL. Out of the 3 cases of *S. aureus* found, 2 were methicillin-resistant. Both *S. pneumoniae* found were resistant to penicillin. The one *E. faecalis* found was sensitive to vancomycin. Out of the 15 found cases of Enterobacteriaceae, 12 were producing ESBL, 2 were not and for one the result of the AST is missing.

Thereby, 80% of the pathogen found where we have the result of the AST would have to be reported to Folkhälsomyndigheten if they were found in Sweden.

**Table 2: Resistance patterns (relevant antibiotics marked in bold style)**

Pathogen	Gender	Site for finding	Resistant	Sensitive	Multi-resistant
<b>Citrobacter</b>	Female	Urine	<b>cepha</b>	amino, BSP, nit, quino	Unknown
<b>E.coli</b>	Male	Pus	BSP, <b>cepha</b> , amino, quino.	carba, chlor.	Yes
	Female	Urine	<b>cepha</b> , nit.	amino, BSP, quino	Yes
	Female	Urine	<b>cepha</b>	amino, nit	Unknown
	Female	Urine	no result	no result	Unknown
<b>E. faecalis</b>	Female	Pus	pen, BSP, <b>cepha</b> , amino, macro, quino	<b>glyco</b> , oxazo	Yes
<b>Klebsiella pneumonie</b>	Male	Pus	BSP, <b>cepha</b> , amino, <b>quino</b>	chlor	Yes
	Male	Sputum	BSP	<b>cepha</b> , chlor, <b>quino</b>	Unknown
	Male	Sputum	BSP, <b>cepha</b>	amino, carba	Unknown
	Male	Sputum	BSP	amino, <b>cepha</b> , <b>quino</b>	Unknown
	Female	Urine	BSP, <b>cepha</b> , amino, <b>quino</b> , chlor	carba	Yes
	Female	Urine	BSP, <b>cepha</b> , amino, <b>quino</b> , chlor	carba	Yes
<b>Providencia</b>	Female	Pus	BSP, <b>cepha</b> , chlor	amino, glyco	Yes
<b>Pseudomonas</b>	Male	Pus	BSP, <b>cepha</b> , <b>quino</b>	amino	Yes
	Male	Pus	BSP, <b>cepha</b>	amino, <b>quino</b>	Unknown
	Female	Urine	<b>cepha</b> , nit	amino, BSP, <b>quino</b>	Yes
<b>S. aureus</b>	Male	Pus	pen	BSP, <b>cepha</b> , glyco, linco, macro, oxaz, quino, tetra	Unknown
	Female	Blood	pen, <b>cepha</b> , macro	amino, glyco, linco, oxaz, rifa	Yes
	Female	Urine	pen, <b>cepha</b> , macro	amino, glyco, linco, oxaz, rifa	Yes
<b>S. pneumoniae</b>	Male	Sputum	<b>pen</b>	linco, tetra	Unknown
	Male	Sputum	<b>pen</b> , macro	amino, <b>cepha</b> , glyco, oxaz	Yes

amino=aminoglycosides, BSP=broad spectrum penicillins, cepha=cephalosporins, glyco=glycopeptides  
linco=lincosamides, macro=macrolides, nit=nitrofurantoin, oxaz=oxazolidiones, pen=penicillin,  
quino=quinolones, rifa=rifampicin, tetra=tetracyclines.



**Figure 15:** Number of multi-resistant bacteria (MRSA, PRSP, VRE and Enterobacteriaceae that produce ESBL) that have to be reported to Folkhälsomyndigheten if found in Sweden

The doctors changed antibiotics after getting the result of the microbial investigation in 10 of the 20 patients with positive bacterial cultures (5 men and 5 women). In the cases where the doctors didn't change antibiotics there were different reasons why they didn't change. In 3 the cases it was because the pathogens were already sensitive to the antibiotics that were given and it was not possible to change to a narrower antibiotic. In one case it would have been possible to change to a narrower drug, but the doctors didn't change the treatment anyway. In one case, the antibiotics that were given as treatment wasn't among the antibiotics that the pathogen was tested for. In one case a pathogen was found but the result of the microbial investigation is missing. In 4 cases the pathogen was resistant to the given treatment, but the treatment wasn't changed anyway.

## Discussion

### Infections and antibiotics

The most common bacterial infections among the patients included in the study was pneumonia or UTI. The antibiotics that were most frequently used were BSP (35%) and cephalosporins (24%). Statistics show that cephalosporins are most frequently used antibiotics in India, followed by BSP (12). If we only chose to include the adults in this study, we see the same trend at KMC. Among the children BSP were the most frequently used antibiotics, as another study from two hospitals in central India also suggests (17). A study from a hospital

in Delhi studies suggests that fluoroquinolones are the most frequently used antibiotics (18). In a study from Ujjain, India, antibiotic use is compared between a teaching hospital and a non-teaching hospital. The results showed that fluoroquinolones and aminoglycosides were the most frequently used antibiotics in the teaching hospital, whereas cephalosporins were the most commonly used antibiotics in the non-teaching hospital (19). In this study the fluoroquinolones were only the third most frequently used antibiotics. Only one patient in the study received tetracyclines. Tetracyclines and penicillins were the two most frequently used antibiotics in Sweden in 2016 (20).

### **Development of antibiotic resistance**

The national guidelines were followed quite well for all the patients with pneumonia or UTI. The guidelines are not very specific though, and many antibiotics are listed as recommended treatment for the infections.

In this study cultures were sent for AST in 57% of the patients that received antibiotic treatment. The percentage is even higher when the children are excluded. This number is however too high, since the doctors asked for cultures specifically for the study so that resistance patterns could be studied. In an earlier study from the same hospital, the cultures sent for AST for the patients receiving antibiotics were 33% (16). The reason why so few cultures were sent for AST within the children's group was because many of the children were only around one year old. That made it difficult, if not impossible, to get good samples.

It is reasonable to have guidelines that include broad-spectrum antibiotics in order to save lives. The problem however is that cultures sent for AST are not taken as a routine and used in the clinical work. According to the Swedish guidelines, cultures should be taken before antibiotic treatment is started in order to receive the best microbiological results. Only 27% of the cultures sent for AST were sent before the antibiotic treatment was initiated. This number can be compared with a repeated nationwide point-prevalence surveys of antimicrobial use in Swedish hospitals between 2003 and 2010, where the results showed that cultures were sent for AST before antibiotic treatment were initiated in 62.1–75.4% of the cases (21). The results of the AST were not always taken into consideration in the clinical work. In 4 cases out of 10, the antibiotics weren't changed although the bacteria turned out to be resistant to the antibiotics given. A possible explanation to why the antibiotics were not changed could be that the patients were already starting to get better. If more cultures were sent for AST, if the cultures were taken before antibiotic treatment started and if the results were taken into larger

consideration in the clinical work, it would be possible to change to narrower antibiotics and thereby slow down the development of MRB.

Another reason for developing MRB is the quite unregulated over-the-counter sells of antibiotics in India (6). A study that included 202 pharmacies in Nagpur, India, between 1988 and 1989 showed that 24.7% of the antibiotics were sold without a doctor's prescription and that 93% of the patients with a prescription didn't know what medicine that had been prescribed (22). Another similar study from 11 pharmacies in Kerala, Southern India, in 2000 show that 18% of the customers purchased antibiotics without a prescription (23). None of the patients in this study reported to have taken any unprescribed antibiotics, however many of the patients reported to have taken some prescribed medicine before coming to the hospital without knowing what it was. Kerala is a state in India where the literacy rate is among the highest in India (24). The high level of education and welfare among the people could contribute to why people seek the medical attention of a doctor rather than buy antibiotics over the counter. Of course the access to a hospital is an important factor as well. Another possibility could be that the patients simply didn't want to admit that they had taken any unprescribed antibiotics.

It is easy to think that the over-counter sales of antibiotics should be prohibited in order to limit the development of MRB. However, we have to take into consideration that many people in India don't have access to health-care. More children still die from the lack of life-saving antibiotics than patients die from MRBs in the hospitals (6). That is a fact that puts the problems into another perspective.

### **Antibiotic resistance patterns**

When focusing on the bacteria that showed resistance patterns that would have to be reported to Folkhälsomyndigheten if they were found in Sweden, we can see that 80% of the found bacteria showed these patterns.

A study from a hospital in Puducherry in southern India suggests that 57.2% of *E. coli* is resistant to beta-lactam antibiotics, 56.0% to cephalosporins, 74.5% to quinolones and 58.2% to aminoglycosides (25). Another study from western India that looked at resistance patterns of *E. coli* and *K. pneumoniae* between 2004 and 2014 showed that 78.4% of the *E. coli* was resistant to extended spectrum cephalosporins and 76.9 to carbapenems (26). In this study,

resistance patterns were found for 3 cultures of *E. coli*. They were all resistant to cephalosporins and one was resistant to aminoglycosides.

Infections caused by multi-resistant *K. pneumoniae* are causing a lot of problems in India. Especially infection with carbapenem-resistant *K. pneumoniae* is a feared disease. The bacteria show various patterns of resistance and according to one study of 567 bacteria colonies between 2012 and 2014, the bacteria showed 13.8% resistance against carbapenems (27). In this study, all the 6 found cases of *K. pneumoniae* were sensitive to carbapenems, however 2 of them were resistant to all antibiotics tested except for carbapenems.

Only 21 pathogens were found, so it is impossible to draw any conclusions about the resistance patterns at the hospital. There were quite a few positive cultures from patients in other wards, that could have been analyzed if out-patients and patients that were not in the medical or pediatric wards would be included in the study. A future study of resistance patterns could therefore possibly use all the positive results found in the microbiological laboratory. However, then it would be very hard to find additional information on the patients not admitted to the hospital.

### **Comparison between men and women**

In the study more women than men were admitted to the general wards of the hospital with the suspicion of an infection; 35 women compared to 27 men. The mean age for the men were 3 years younger than for the women and the average length of stay were 1,1 days longer for the women. Kerala is a state in southern India where there are more women than men (28), which could be one of the reasons why more women were admitted. Another possibility could be that women are more prone to getting infections, especially UTIs, which were the dominating reason why women got admitted. The difference in the length of the stay could possibly be explained by the age difference between the two patient groups.

In the male group, the most common comorbidity was COPD; 33% of the men suffered from COPD compared to 11% of the women. That makes them more prone to getting respiratory tract infections such as pneumonia, which was the most common reason for admission among the men.

Another interesting observation was that 43% of the women in the study suffered from hypertension, while only 19% of the men suffered from the same. Could it be that a higher blood pressure was expected for the men and not written down in the medical file? Or do men

more often receive antihypertensive medicine than women? That could also be a subject for further investigation.

In the study from 11 pharmacies in Southern India, the result showed that 57% of the sold medicine were given to male patients (23). In this study however, there was no large difference in how many antibiotics men were prescribed compared to women. On the other hand, there were differences in what kind of antibiotics that were prescribed. The difference can however easily be explained when we look at what kind of infections the both groups were admitted for. Men also tended to receive more intravenous antibiotics than women.

Another observation was that 22% of the men and 29% of the women chose to pay extra money to stay in private wards. A subject for further investigation could be to see if there are any differences in the treatment between the patients that stay in the private wards compared to the general wards.

### **Strengths and weaknesses**

There are several limitations within the study. One is the difficulty of gathering correct data. The medical files at the hospital are handwritten and the same antibiotics can have many different names. Especially in the beginning it was hard to understand if the patient received antibiotics or not, since a lot of patients received a long list of medicines under brand names that are only used in India. Some names of antibiotics are very similar to other drugs names, which made it hard to know if the patient received antibiotics if the doctor's handwriting was bad. The nurses and junior doctors were very helpful, but there might still be errors where drugs are missed or wrongly interpreted.

The question whether the patients had taken any other antibiotics before getting admitted was asked by the nurses in Malayalam. In many cases the answers were not very convincing. A lot of patients said that they had seen a doctor before getting admitted and that they had received some medicine, but they didn't know what medicine it was. Some patients answered no at first, but then some member of the family came and handed a chart from another doctor where we could see that antibiotics were subscribed.

Another problem is the limited amount of patients included in the study. Since only 84 patients were included, one patient accounts for just above 1% of the study population. The low number of patients makes it very hard to find statistical significance. If a larger number of patients were included in the study, statistical significance could easier be found.



## Summary

The most common infections were pneumonia and UTI. The most frequently used antibiotics were BSP and cephalosporins. Almost all prescribed antibiotics were in accordance with the national guidelines, however the guidelines are not very specific. Cultures were sent for AST in 57% of the patients, but that percentage is too high since cultures were sent especially for this study. In 73% of the cases where cultures were sent for AST, the cultures were sent after the antibiotic treatment was initiated. The results of the AST were only taken into consideration in the clinical work in 50% of the cases. Out of the pathogen found, 80% showed resistance patterns that would have to be reported to Folkhälsomyndigheten if they were found in Sweden. The differences in antibiotic treatment between men and women could be explained by the fact that they were admitted for different types of infections.

## Conclusion

The main problem is that cultures are not taken in an optimal way and that they are not sent for AST as a routine. Furthermore, the results are not always used to change into narrower antibiotics and thereby limit the development of multi-resistant bacteria (MRB)

## Antibiotikaresistens –användningen av antibiotika i relation till riktlinjer och resistensmönster

Antibiotika används för att bota och förebygga bakteriella infektioner. Antibiotikaresistens inträffar naturligt, men felaktig och överdriven användning av antibiotika snabbar på processen. Idag ökar antibiotikaresistensen i oroväckande takt och har blivit ett av de största hoten mot modern medicin. Indien är det landet i världen som totalt använder mest antibiotika. Antibiotika har länge kunnat säljas helt okontrollerat utanför sjukhusen i landet.

Det finns olika sätt att minska utvecklingen av resistent bakterier. Det viktigaste är att använda antibiotika på ett effektivt sätt. Det finns många olika typer av bakterier och de är känsliga mot olika sorter av antibiotika. Vissa antibiotika biter på många olika bakterier och det är viktigt att dessa breda antibiotika inte används för mycket. Om bakterierna blir resistent mot våra bredaste antibiotika har vi inget medel att ge för att bota livshotande bakteriella infektioner. Det finns riktlinjer för antibiotikaanvändning för att underlätta valet av behandling.

Ett sätt att minska resistensutvecklingen är att ta prover och skicka för bakterieodling och resistensbestämning. Då kan man se vilka antibiotika bakterien som gör patienten sjuk är känslig för. Det gör det möjligt att byta till ett så smalt antibiotika som möjligt och ändå bekämpa infektionen på ett effektivt sätt.

I den här studien har antibiotikaanvändningen på Kannur Medical College, Super Specialised Hospital undersökts. Vi kan se att lunginflammation och urinvägsinflammation är de vanligaste infektionerna hos patienterna som ligger inne på sjukhuset. Läkarna följer de nationella riktlinjerna avseende antibiotikaanvändning, men riktlinjerna är inte så specifika. Bakterieodlingar tas inte som rutin och används inte i det kliniska arbetet i den utsträckning som de kunde. Vi kan också se att 80% av de funna bakterierna uppvisar resistensmönster som är anmälningspliktiga enligt svenskt regelverk.

Om fler odlingar togs på patienterna och svaren användes i en större utsträckning skulle det vara möjligt att byta till smalare antibiotika och därmed begränsa utvecklingen av resistent bakterier.

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## Figures and tables

**Figure 1:** Percent of patients with different comorbidities. Men and women illustrated separately.

**Figure 2:** Types of infections in percent. Men, women and children illustrated separately.

**Figure 3:** Percent of patients that received 1, 2 or 3 antibiotics. Men, women and children illustrated separately.

**Figure 4:** Percent of antibiotics used as first treatment divided into groups of antibiotics with similar molecular targets

**Figure 5:** Percent of types of antibiotics used as first treatment. Men, women and children illustrated separately.

**Figure 6:** Administration ways of given antibiotics in percent. Men, women and children illustrated separately.

**Figure 7:** Total antibiotics used for pneumonia.

**Figure 8:** Antibiotics used in total for UTI and pneumonia and/or UTI.

**Figure 9:** Antibiotics used in total skin infections.

**Figure 10:** Percent of cultures taken and sent for antimicrobial susceptibility testing (AST). Men, women and children illustrated separately.

**Figure 11:** Culture sites in all patients.

**Figure 12:** Culture sites illustrated separately for men, women and children.

**Figure 13:** Cultures sent for in relation to start of antibiotic treatment in percent illustrated separately men, women and children.

**Figure 14:** Number of pathogen found, men and women illustrated separately.

**Figure 15:** Multi-resistant bacteria (MRSA, PRSP, VRE and Enterobacteriaceae that produce ESBL) that have to be reported to Folkhälsomyndigheten if found in Sweden.

**Table 1:** Types of antibiotics used.

**Table 2:** Resistance patterns (relevant antibiotics marked in bold style).



## Appendices - Form

**Date of admission:**

### **Antibiotic resistance – a descriptive study at Kannur Medical College**

**Hospital I.D:**

**Patient number:**

**Gender:**

**Ward:**

**Age:**

**Temperature > 38,0°C or <35,5°C (YES or NO)**

**Signs of infection:**

**Suspected site of infection:**

**Antibiotics received (date of commencement, dose and administration type):**

**Other antibiotics taken before getting admitted (prescribed or not prescribed):**

**Other diseases:**

**Change of antibiotics:**

**Date of culture and culture sites:**

**Pathogen found and site for finding:**

**Antibiotic resistance pattern:**

**Date of discharge from hospital:**