ANTIBIOTIC/ANTIMICROBIAL RESISTANCE PATTERNS OF BACTERIAL PATHOGENS ISOLATES FROM NATIONAL RESEARCH CENTER FOR MOTHER AND CHILD HEALTH IN ASTANA, KAZAKHSTAN

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Table of content

ABBREVIATION LIST

AMR - antimicrobial resistance

MDR - multidrug resistance

XDR -extremely drug resistant

PDR - pan-drug resistant

ICU - intensive care unit

MRSA - methicillin-resistant *Staphylococcus aureus*

VRE - vancomycin-resistant Enterococci

CA-LRTIs - community-acquired low respiratory tract infections

GLASS - global antimicrobial resistance surveillance system

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ABSTRACT

Introduction

The rapid emergence of drug resistant bacteria is occurring worldwide, endangering the efficacy of antibiotics, which have transformed medicine and saved millions of lives (1-6). Many decades after the first patients were treated with antibiotics, bacterial infections have again become a threat (7). The antibiotic resistance crisis has been attributed to the overuse and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry due to reduced economic incentives and challenging regulatory requirements.

Materials and methods: This cross-sectional study, observational study was performed from January 2015 through August 2017 in the National Research Center of Mother and Child health, which is a tertiary care teaching hospital, in Astana, Kazakhstan. A total number of patients 10,000 were admitted to the Mother and Child Center annually. The study protocol was approved by the Research Ethics Committee of Nazarbayev University. All patients were screened for the presence of antibiotic resistant pathogens. Antibacterial therapy was prescribed if indicated and cultures were requested when infection was suspected. Regular investigations were performed following international guidelines. All personal information was excluded from the records.

Results

Out of 2,937 samples analyzed, 649 (22.10%) showed significant growth of organisms that exhibited multiple drug resistance. *Escherichia coli* was the most common MDR organism isolated with a total of 141 (21.73%), followed by *Klebsiella pneumoniae* 133 (20.49%). Most isolates were cultured from the throat (1,573 which is equivalent to 53.56% of total culture-positive samples) and urine (493 or 16.70%).

Categorizing specimen type distribution of samples by Hospital unit, most of culture-positive samples came from urine in Mother ICU 22 (59.4%), Uronephrology 252 (64.8%) and Surgery Unit 23 (27.4%). In Neonatology ICU the majority of culture-positive samples were from blood 27 (60%). The most of pathogen-containing samples were isolated from the throat in Pediatric ICU 92 (23.6%), in Oncology Unit 748 (65.6%), in Rheumatology unit 246 (92.5%), in Therapeutic unit 387 (75.7%). The majority of samples that came from cervix were in Gynecology unit 45 (60%).

E. coli and *Pseudomonas aeruginosa* were the most common MDR pathogen isolated from abdominal cavity 3 (37.5%), stool 3 (30%) and urine 101 (51.3%). *Pseudomonas aeruginosa* has an increase in multidrug resistance which was 6.73% of the total number of culture-positive for *Pseudomonas aeruginosa* samples isolated in 2015, 10.43% out of total number isolated in 2016, 19.59% out of total number isolated in 2017. *Streptococcus mitis* showed no considerable resistance to any of the antibiotics including penicillin, and was only 4.24%. *Staphylococcus aureus* was resistant to Penicillin in 97.4% cases and to Ampicillin in 87.09% cases, Amoxicillin in 90% cases; *Streptococcus epidermidis* was resistant to Penicillin in 97.67% cases. Age distribution of multidrug resistant pathogens was equal among all four age groups. 0-5 years old group had 21.47% of MDR, while 5-12 years was 24.87%, 12-18 years as 20.63%, and finally more than 18 years was 20.25%. Among all age groups, multidrug resistance of each pathogen also was distributed equally without any patterns to stand out.

Conclusions. Based on the findings, there is a need to further research to find reasons and possible measures to combat increased MDR in Neonatology ICU and other hospital units with elevated MDR prevalence. Also, *Streptococcus mitis* should not be tested extensively for drug resistance, since the majority of isolated strains were sensitive to penicillin. Increase in prevalence of MDR *Pseudomonas aeruginosa* with time need to be closely monitored

further. In addition, further research is needed to confirm trends of the prevalence of MDR. Due to difficulties with standardized data collection, central monitoring system is necessary for standardized data collection and analysis

INTRODUCTION

Antimicrobial resistance (AMR) is the development of resistance in microorganism which are bacteria, viruses, fungi and parasites, to an antimicrobial drug to which it was previously sensitive. AMR in a wide range of infectious pathogens is a growing public health threat that is of a great concern to countries and many sectors. The rapid rate of growth is especially alarming because of the global spread of multi-resistant bacteria that cause common infections and that resist treatment with existing antimicrobial agents (41).

Antimicrobial resistance is an internationally recognized public health problem. The contribution of primary health care is particularly considerable as this is where almost 80% of all antibiotic agents used within the health service are prescribed (8). Resistant to antibiotics, bacterial infections can limit the availability of effective treatment options, altering some commonly encountered bacterial infections troublesome to treat, including those causing infections of the urinary tract. Antibiotic resistant infections also increase morbidity and mortality two-fold and are associated with increased healthcare costs (9). In low income countries, affordability of second line drugs and restricted access to healthcare can limit the use of newer broad-spectrum antibiotics, causing growing concerns for increased morbidity and mortality from antibiotic resistant infections in these countries (10).

Children receive a lot of primary healthcare services and as such, receive a considerably high number of antibiotics compared with middle age groups (11). Children are also key drivers of infection within communities and can contribute to the spread of bacteria from person to person. Despite this, there is limited number of studies has been published describing the prevalence of bacterial resistance in children or the risk factors of importance in this group. In 2010, Costelloe and colleagues conducted a systematic review that reported strong

associations between previous encounter to routinely prescribed antibiotic agents in primary care and antimicrobial resistance persisting for up to 12 months (12). Most of the contributing studies, however, were conducted in adults.

The antibiotic resistance associated with CA-LRTIs varies significantly depends on geographical locations and investigated populations (32, 33). Therefore, it is not adequate to simply copy the existing guidelines from other countries, which may be inappropriate and lead to serious problems in clinical practice (30).

Urinary tract infections are one of the most common bacterial infections seen in primary care (13). In children with a suspected urinary tract infection, the most common approach is to treat empirically with an antibiotic while expecting for results of culture and sensitivity testing. Young children are more vulnerable to immediate and long-term complications, including renal scarring and renal failure, (14) and therefore require prompt and appropriate treatment. *Escherichia coli* is responsible for over 80% of all urinary tract infections (15) and is also the most common cause of bacteremia and foodborne infections and a cause of meningitis in neonates (16).

Reasons for why antibiotic resistance is a concern

In many other countries, antibiotics are poorly regulated and available over the counter without a prescription (19, 24). This lack of regulation leads to that antibiotics that are easily accessible, abundant, and affordable, causing overuse (24). The ability to obtain such products online has also made them easily accessible in countries where antibiotics *are* regulated (24). Incorrectly prescribed antibiotics also contribute to the promotion of resistant bacteria (5). Studies have shown that treatment indication, choice of agent, or duration of antibiotic therapy is incorrect in 30% to 50% of cases (5, 27). One U.S. study reported that a pathogen was defined in only 7.6% of 17,435 patients hospitalized with

community-acquired pneumonia (CAP) (23). In comparison, investigators at the Karolinska Institute in Sweden were able to identify the probable pathogen in 89% of patients with CAP through use of molecular diagnostic techniques (polymerase chain reaction [PCR] and semiquantitative PCR) (23). In addition, 30% to 60% of the antibiotics prescribed in intensive care units (ICUs) have been found to be unnecessary, inappropriate, or suboptimal (27). Incorrectly prescribed antibiotics have questionable therapeutic benefit and expose patients to potential complications of antibiotic therapy (20). Subinhibitory and subtherapeutic antibiotic concentrations can promote the development of antibiotic resistance by supporting genetic alterations, such as changes in gene expression, HGT, and mutagenesis (17). Changes in antibiotic-induced gene expression can increase virulence, while increased mutagenesis and HGT promote antibiotic resistance and spread (17). Low levels of antibiotics have been shown to make contribution to strain diversification in organisms such as *Pseudomonas aeruginosa* (17)

Discovery of new antimicrobial agents is not a solution

Antibiotic development is no longer considered to be an economically beneficial investment for the pharmaceutical industry (23). This statement is supported by the fact that antibiotics are used for relatively short periods and are often curative. Furthermore, antibiotics are not as profitable as drugs that treat chronic conditions, such as diabetes, psychiatric disorders, asthma, or gastroesophageal reflux (1, 3, 22, 23). A cost–benefit analysis by the Office of Health Economics in London estimated that the net present value (NPV) of a new antibiotic agent is only about $50 million, in comparison with approximately $1 billion for a drug used to treat a neuromuscular disease (23). Medicines for chronic conditions are more profitable, for this reason pharmaceutical companies prefer to invest in them (2).

When new agents are eventually used, the emergence of resistance is nearly unavoidable (2). However, since bacterial evolution is uncertain, the timeline for the development of resistance is unpredictable (2). A manufacturer that invests their finances into antibiotic development may therefore discover that profits are prematurely curtailed when resistance develops to a new antibiotic (2).

Among gram-positive pathogens, a global pandemic of resistant *S. aureus* and Enterococcus species currently poses the biggest threat (5, 25). MRSA kills more Americans each year than HIV/AIDS, Parkinson's disease, emphysema, and homicide combined (1, 21). Vancomycin-resistant enterococci (VRE) and a growing number of additional pathogens are developing resistance to many common antibiotics (1).

Gram-negative pathogens are particularly worrisome because they are becoming resistant to nearly all the antibiotic drug options available, creating situations reminiscent of the pre-antibiotic era (1, 5, 25). The emergence of MDR (and increasingly pan-resistant) gram-negative bacilli has affected practice in every field of medicine (1). The most serious gram-negative infections occur in health care settings and are most commonly caused by Enterobacteriaceae (mostly *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* (5, 25)). MDR gram-negative pathogens are also becoming increasingly prevalent in the community (25).

MDR Pseudomonas Aeruginosa

P. aeruginosa is a common cause of HAIs, including pneumonia and bloodstream, urinary tract, and surgical-site infections (5). More than 6,000 (13%) of the 51,000 healthcare–associated *P. aeruginosa* infections that occur in the U.S. each year are MDR (25). Roughly 400 deaths per year are attributed to these infections (5). Some strains of MDR *P.*

aeruginosa have been found to be resistant to nearly all antibiotics, including aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems (25).

MDR Acinetobacter baumannii

Acinetobacter is a gram-negative bacterium that causes pneumonia or bloodstream infections, especially in critically ill patients on mechanical ventilation (5). Some *Acinetobacter* species have become resistant to all or nearly all antibiotics, including carbapenems, which are often considered to be the drug of last resort (5). About 12,000 health care acquired *Acinetobacter* infections occur in the U.S. each year, and 7,300 (63%) of these are MDR (resistant to at least three different classes of antibiotics), causing 500 deaths per year (5).

Multidrug resistance definition

The definition of MDR is very vague; therefore, there is a need to form clear understanding what MDR is in this study. In literal terms, multidrug resistance means 'resistant to more than one antimicrobial agent', but a standardized definition for MDR has not yet been agreed upon by the medical community. There are many definitions that are currently being utilized to characterize patterns. The most practical definition used for Gram-positive and Gram-negative bacteria is 'resistant to three or more antimicrobial classes'. Selecting Gram-negative isolates resistant to 1^{st} and 2^{nd} line antibiotics by standard disk diffusion test was very difficult as isolates were from different sites which had different antibiotics in their 1^{st} and 2^{nd} line of treatment (30).

The antibiotic resistance associated with CA-LRTIs varies significantly depends on geographical locations and investigated populations (32, 33). Therefore, it is not adequate to

simply copy the existing guidelines from other countries, which may be inappropriate and lead to serious problems in clinical practice (30).

Many different definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria are being utilized in the literature to distinguish the different patterns of resistance found in healthcare-associated, antimicrobial-resistant bacteria. A group of international experts came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), to form a standardized international terminology with which to characterize acquired resistance profiles in *S. aureus*, Enterococcus spp., Enterobacteriaceae (other than Salmonella and Shigella), *P. aeruginosa* and Acinetobacter spp., all bacteria often responsible for healthcare-associated infections and incline to become multidrug resistant. Epidemiologically significant antimicrobial categories were constructed for each bacterium. Lists of antimicrobial categories proposed for antimicrobial susceptibility testing were created using documents and breakpoints from the Clinical Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the United States Food and Drug Administration (FDA). MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and PDR was defined as non-susceptibility to all agents in all antimicrobial categories. To ensure correct application of these definitions, bacterial isolates should be tested against all or nearly all of the antimicrobial agents within the antimicrobial categories and selective reporting and suppression of results should be avoided (34).

Global monitoring systems of antimicrobial resistance

Information to monitor and manage this spread exists in the susceptibility test results of tens of thousands of laboratories worldwide. The comparability of those results is uncertain, however, and their storage in paper files or in computer files with diverse codes and formats has made them inaccessible for analysis. The WHONET program puts each laboratory's data into a common code and file format at that laboratory, either by serving as or by translating from its own computer reporting system. It then empowers each medical center to analyze its files in ways that help it monitor and manage resistance locally and to merge them with files of other centers for collaborative national or global surveillance of resistance (35). Such data management strategy is currently lacking in Kazakhstan.

The Global Antimicrobial Resistance Surveillance System (GLASS) is being developed to support the Global Action Plan on Antimicrobial Resistance and should be coordinated within the national action plans of countries. The goal of GLASS is to enable standardized, comparable and validated data on AMR to be collected, analyzed and shared with countries, in order to inform decision-making, drive local, national and regional action and provide the evidence base for action and advocacy (36).

Even though Kazakhstan is a member or participant in global resistance monitoring systems, there is no reports on antimicrobial resistance situation available. The implementation of the monitoring systems is in progress at the moment. Furthermore, there is lack of published data on antibiotic resistance topic in Kazakhstan.

AIM OF THIS STUDY

This study aims to analyze patterns of the common pathogens in the Mother and Child Hospital in Astana, Kazakhstan. For establishing these patterns, the study is developed to find associations between multidrug resistance and 4 variables at the study site such as type of pathogen, hospital unit, type of specimens, age. Based on the findings, the study will form guidelines to provide recommendations for antimicrobial stewardship programs in the Mother and child hospital. Furthermore, the study aims to provide guidance for effective antibiotic choice. By implementing antimicrobial stewardship program, the ultimate goal is to minimize the development of antimicrobial and multidrug resistance.

METHODS

An observational study was conducted for a period of 2 years and 8 months from January 2015 to August 2017 in a tertiary care hospital in Astana, Kazakhstan. Approval from the Institutional Research and Ethical committee was obtained prior to the commencement of the study. Data regarding culture and sensitivity of the organisms isolated from different sources such as urine, blood, pus/wound/skin, stool, sputum, cervix, nose swabs were collected from the records of the State Diagnostic Center (Microbiology laboratory). Sample processing, identification of organisms to the genus and/or species level and antimicrobial sensitivity were carried out as per the Clinical and Laboratory Standards Institute guidelines on the 2,937 samples received.

Data collection

A cross-sectional observational study was conducted between January 2015 and August 2017. The initial number of medical records was close to 7000. Due to errors in data entry (mostly because of non-standard methods of data collection), many records not relevant to this study were omitted.

Some samples were tested for the presence of drug resistance for certain antibiotics, other samples for another antibiotic. Each individual pathogen has been tested for a particular set of antibiotics, but not all for the antibiotics in this set. In other words, the number of samples of a certain pathogen varied across different antibiotics.

Age-stratification was done by 5-7 years in order to make each age group similar in the number of participants as well to have biological similarities.

Inclusion criteria

The inclusion criteria were that the patients are only from Mother and Child Center. Initial data consisted of over 40 pathogens, but due to small number of representatives for each pathogen (small sample size) these were deleted from this study. Only 12 pathogens were included in the study as they had sample size enough to perform statistical analysis to obtain statistical significance. Samples that were culture-positive for 12 pathogens were included in the study. In addition, age was the inclusion criteria, though many medical records contained incorrect age. Also, Mother and Child Health Center has over 20 hospital units, data from some of the units were combined in one category. For example, data from urology, nephrology and kidney center were combined into one Uronephrology unit category. There are 4 different oncology units that data were combined into one oncology unit category. In the Mother and Child health center, data from obstetrics and gynecology units was combined into one gynecology unit category.

Due to inconsistency in data entry, specimens were named differently. By researcher's judgement, main categories were established. As an example, nasal swab, nose, nostrils, nasal discharge was combined into one category "nose". Many medical records were deleted as they could not be attributed to any of the categories such as drainage, since no clear information was available about the exact location where the drainage came from.

Exclusion criteria

Culture-positive for pathogens not selective for this study, or negative culture were deleted. Also, repetitive testing is a normal practice for hospitals. These medical records were also excluded from the study, as they inflated the number of culture-positive and/or multidrug resistant samples leading to incorrect results.

Secondary data was used for this study. The data entry occurred as the Department of Infection Control in Mother and Child Health Center had access to the medical records. It contained laboratory testing results with the pathogen that the patient was positive to, and antibiotics that the pathogen was either sensitive, resistant or intermediate. Intermediate were assumed as resistant, since some of the resistance was present though not to the full extent. These laboratory testing records were collected into one database for further analysis on prevalence, distribution and antimicrobial resistance monitoring.

Sample

All medical records belong to the Mother and Child Center patients. The results obtained were of samples from patient blood, urine, nose, throat testing results. These samples were from patients from all hospital units of Mother and Child Center. Age of the participants were in the range of 0-47 years. Convenience sampling was used to collect data. As it was discussed above, only those records that were available with full set of information were included. Sample size contained 2,937 of culture-positive samples, whereby out of this number, 649 of these pathogens were multidrug resistant.

No tentative sample size calculation was made, since the sampling was convenient. In other words, all medical records that met the study requirements were included in the study.

Also, there is important to note that the cutoff level for the pathogen was established as 50 counts. This was done for the purpose of feasibility of the study as much as obtain statistical significance.

Statistical analysis

STATA SE 12.0 package was used for frequencies and percentage for categorical variables, chi square. Poisson regression with robust equal variance was used to establish the association of multidrug resistance development and types of hospital units.

Variables

Dependent variable was the presence or absence of multidrug resistance while the Independent variables were pathogen types, specimen type, hospital units, and patients' age (in years).

Antibiotics tested for sensitivity against gram negative bacteria were erythromycin, penicillin, oxacillin, clarithromycin, ampicillin, cefazolin, gentamycin, azithromycin, amoxicillin, ceftazidime, piperacillin, clindamycin, trimethoprim, vancomycin, doxycycline, tetracycline, piperacillin, linezolid, amoxicillin, cefepime, cefotaxime, meropenem, ceftriaxone, ertapenem, aztreonam, amikacin, imipenem, ciprofloxacin, cefuroxime, ticarcillin, levofloxacin, lomefloxacin, moxifloxacin, tobramycin, minocycline, norfloxacin, chroramphenicol, and ofloxacin.

Organisms considered to be multidrug resistant to Gram-positive and Gram-negative bacteria is 'resistant to three or more antimicrobial classes'. Selecting Gram-negative isolates resistant

to 1st and 2nd line antibiotics by standard disk diffusion test was very difficult as isolates were from different sites which had different antibiotics in their 1st and 2nd line of treatment (30).

ETHICS

No personally identifiable data was obtained during the study. After getting an informed consent from the subjects, they were requested to answer a simply formulated questionnaire to the fullest of their knowledge to elicit their prior antibiotic history. Other relevant data was obtained from the patient's case sheet.

RESULTS

The total number of samples sent to the microbiology laboratory from Mother ICU, Neonatology ICU, Pediatric, Uronephrology, Gynecology, Oncology, Therapeutic, Rheumatology, Surgery units for culture and sensitivity during the period from January 2015 to August 2017 was 2,937 samples. Out of this (TABLE 1), 37 (1.26%) samples were from patients hospitalized in Mother ICU, 45 (1.53%) from Neonatology ICU, 390 (13.28%) from Pediatric ICU, 389 (13.24%) from Uronephrology unit, 75 (2.55%) from Gynecology unit, 1140 (38.82%) from Oncology unit, 266 (9.06%) from Rheumatology unit, 511 (17.4%) from Therapeutic unit, 84 (2.86%) from Surgery Unit. Out of 2,937 samples, 649 (22.10%) showed significant growth of organisms exhibiting multiple drug resistance. Out of these, 20 were (3.08%) from Rheumatology unit, 9 (1.4%) from Mother ICU, 31 (4.78%) from Neonatology unit, 146 (22.5%) from Pediatric unit, 132 (20.34%) from Uronephrology unit, 12 (1.85%) from Gynecology unit, 182 (28.04%) Oncology unit, 78 (12.02%) from Therapeutic unit, and 39 (6%) from Surgery unit.

Streptococcus mitis was the most common isolate (1085 (36.96%)), *Staphylococcus aureus* (389 (13.24%)), *Staphylococcus epidermidis* (230 (7.83%)), *Escherichia coli* (222 (7.56%)), *Candida albicans* (208 (7.08%)), *Pseudomonas aeruginosa* (198 (6.74%)), *Klebsiella pneumoniae* (193 (6.57%)), *Enterococcus faecalis* (188 (6.4%)), *Acinetobacter baumannii* (83 (2.83%)), *Streptococcus pneumoniae* (50 (1.7%)), *Candida tropicalis* (50 (1.7%)), and *Stenotrophomas maltophilia* (41 (1.4%)) (Table 2*).* *Escherichia coli* was the most common MDR organism isolated with a total of 141 (21.73%), followed by *Klebsiella pneumoniae* (133 (20.49%)), *Staphylococcus epidermidis* (109 (16.8%)), *Pseudomonas aeruginosa* (73 (11.25%)), *Staphylococcus aureus* (73 (11.25%)), *Acinetobacter baumannii* (29 (4.47%)), *Candida albicans* (27 (4.16%)), *Stenotrophomonas maltophilia* (24 (3.7%), *Enterococcus faecalis* 18 (2.77%)), *Candida tropicalis* (10 (1.54%)), *Streptococcus mitis* (12 (1.85%)), and *Streptococcus pneumoniae* showed no multidrug resistance.

In Mother ICU, the most common isolate was *E. coli* (10 (27%)), while *Staphylococcus epidermidis* was14 (31%)), in Neonalogy ICU, *Pseudomonas aeruginosa* was 62 (16%) in Pediatric ICU and 15 (17.86%) in Surgery unit, *E. coli* was 93 (23.9%) in Uronephrology, *Enterococcus faecalis* was 27 (36%) in Gynecology, *Streptococcus mitis* was 578 (50.7%) in Oncology unit and 251(49%) in Therapeutic unit, and 136 (51%) in Rheumatology unit (Table 3)

Most isolates were cultured from the throat with 1,573 (53.56%), urine was 493 (16.70%), nose 197 (6.71%), blood 166 (5.65%), and wound/skin/pus 152 (5.18%), following intubation tube, sputum, cervix, subclavian catheter, urine catheter, nasogastric tube, stool, abdominal cavity (Table 4). Most MDR isolated were cultured from urine which == (30.35%), throat 138 (21.26%), blood 83 (12.79%), pus/wound/skin 51 (7.86%), intubation tube 45 (6.93%), nose 44 (6.78%) following subclavian catheter, sputum, nasogastric tube, urine catheter, abdominal cavity, breast milk, cervix, stool.

Streptococcus mitis was cultured from the throat with 1017 (64.7%) and sputum was 31 (40.8%), *Enterococcus faecalis* from cervix was 27 (49%), urine catheter was 10 (32.3%), *E. coli* from abdominal cavity was 5 (41.7%), stool 5 (27.8%), urine 160 (32.5%), *Pseudomonas aeruginosa* from intubation tube 24 (27.6%) and nasogastric tube 7 (31.8%), *Staphylococcus aureus* from nose 85 (43.1%) and pus/skin/wound 40 (26.3%), *Staphylococcus epidermidis* from blood 65 (39.2%), subclavian catheter 20 (41.5%) (Table 5).

Most of culture-positive samples came from urine in Mother ICU (22 (59.4%)), Uronephrology (252 (64.8%)), Surgery Unit (23 (27.4%)); in Neonatology ICU from blood (27 (60%)); from the throat in Pediatric ICU (92 (23.6%)), in Oncology Unit (748 (65.6%)), in rheumatology unit (246 (92.5%)), in Therapeutic unit (387 (75.7%)); and from cervix in Gynecology unit was 45 (60%) (Table 6).

In Mother ICU, the most common MDR isolate was *Escherichia coli* 3 (33%) in Uronephrology 64 (48.5%) and Gynecology 4 (33.3%), *Klebsiella pneumoniae* in Pediatric ICU 33 (22.6%) and Oncology unit 39 (21.5%), *Pseudomonas aeruginosa* 14 (35.9%) in Surgery unit, *Staphylococcus aureus* in Therapeutic unit 19 (24.4%) and Rheumatology 14 (70%), *Staphylococcus epidermidis* in Neonatology ICU 11 (35.5%) and Oncology unit 40 (22%) (TABLE 7).

E. coli and *Pseudomonas aeruginosa* were the most common MDR pathogen isolated from abdominal cavity (3 (37.5%)), stool (3 (30%)) and urine (101 (51.3%)); MDR *K. pneumoniae* from subclavian catheter (9 (33.3%)) and ng tube (3 (27.2%)), MDR *Staphylococcus epidermidis* from blood (50 (60.24%)) and nose (20 (45.45%)), MDR *Staphylococcus aureus* from throat (45 (32.6%)), MDR *Pseudomonas aeruginosa* from intubation tube (15 (33.3%)), urine catheter (5 (55.6%)), and sputum (4 (28.57%)) (Table 8).

In Rheumatology unit (16 (80%)), in oncology unit (50 (27.5%)), (41 (52.6%)) in Therapeutic unit from the throat of samples contained MDR pathogens, in Neonatology ICU (18 (58%)) from blood, in Pediatric ICU (24 (16.4%)) from urine, in Uronephrology Unit (112 (84.8%)) from urine, in gynecology unit (7 (58.3%)), in surgery unit (11 (28.2%)) from pus/wound/skin (Table 9).

(Figure 1 and Table 15) Looking at the dynamics in each pathogen separately, there is a drop in Multidrug resistance of *S. mitis* from 4.48% in 2015, 0.72% in 2016 to 0% in 2017; of *Candida albicans* from 8.52% in 2015, 2.52% in 2016 to 0.68% in 2017, *Enterococcus faecalis* showed some drop from 5.38% (2015) to 1.08% (2016), and relatively little increase of 2.03% in 2017. *Pseudomonas aeruginosa* had an increase in multidrug resistance which was 6.73% in 2015, 10.43% in 2016, 19.59% in 2017. The rest of the pathogens did not demonstrate any either positive or negative dynamism. Limitation was that with only 2.5 years study, this was not long enough a period of time to notice remarkable changes.

Drug-specific resistance

(Table 10) *Streptococcus mitis* showed no considerable resistance to any of the antibiotics including penicillin, which only 4.24%. *Streptococcus pneumoniae* was sensitive to almost all antibiotics tested for sensitivity, except against Trimetoprim/sulfomethoxazol with 40% resistance. *Enterococcus faecalis* demonstrated the highest resistance to Norfloxacin (25%) and Penicillin (18.33%); *Staphylococcus aureus* resistant to Penicillin in 97.4% cases and to Ampicillin in 87.09% cases, Amoxicillin in 90% cases; *Streptococcus epidermidis* is resistant to Penicillin in 97.67% cases, to Erythromycin in 50% tests, and to Clarithromycin, Trimetoprim/Sulfomethoxazol, Azithromycin approximately in 48% cases.

(Table 11) *Acinetobacter baumannii* was resistant in 1/3 cases to ceftazidime, trimethoprim/sulfomethoxazol, piperacillin, ampicillin/sulfomethoxazol, cefepime, cefuroxime, ceftriaxone, and in 44.44% cases for ticarcillin/clavulanate.

E. coli was resistant in 97 % to ampicillin and amoxicillin, in about 60-70% of cases to cefazolin, piperacillin, ampicillin/sulfomethoxazol, amoxicillin/clavulanate, ticarcillin/clavulanate, trimethoprim.

Klebsiella pneumoniae was resistant to ampicillin in 99.48% and 100% to amoxicillin, approximately 70-80% cases to cefazolin, piperacillin, amoxicillin/clavulanate, ampicilline/sulfomethoxazol, cefuroxime, ticarcillin/clavulanate.

Pseudomonas aeruginosa appeared to be resistant to ceftazidime in 44.57%, gentamycin 34.57%, piperacillin in 32.95%, cefepime 32.82%.

Stenotrophomas maltophilia was resistance to ticalrcillin/clavulanate in 76.92% and to ceftazidime in 60% cases.

(Table 12) For yeast infections such as *Candida albicans* and *Candida tropicalis* less resistance was for Amphotericin 1.13% and 11.63% respectively, and no resistance to nystatin.

(Table 13) Age distribution of multidrug resistant pathogens was equal among all four age groups. 0-5 years old 21.47%, 5-12 years 24.87%, 12-18 years 20.63%, more than 18 years 20.25% Among all age groups, multidrug resistance of each pathogen also was distributed equally without any patterns to stand out. Contingency table indicates p-value of 0.161 meaning that no association between developing drug-resistance and patients' age.

(Table 14) Rheumatology unit has the lowest prevalence of MDR therefore it was selected as reference to compare with MDR prevalence in other hospital units. The results of Poisson

regression indicated that Neonatology ICU has 9 times more MDR prevalence , 6 times more in Surgery Unit, almost 5 times more in Pediatric ICU than in Rheumatology Unit.

Maximum resistance was observed with commonly used first line antimicrobials such as co-trimoxazole, penicillin, ampicillin, amoxicillin, amoxiclav, piperacillin. Least resistance was observed in third generation cephalosporins, fluoquinolones, meropenem, linezolid, amikacin, vancomycin.

DISCUSSION

The results obtained are discussed below categorized by the pathogens selected for this study. 1) *Streptococcus mitis* was the most common culture-positive isolate 1,085 (36.84%). It has one of the least MDR prevalence rate (1.1%). *St. mitis* has only 4.24% resistance to Penicillin, making this antibiotic is a good choice for treating patients with *St. mitis* caused infections. *St. mitis* was mostly isolated from the throat. This pathogen is leading in culture-positive isolates in Rheumatology (51%), Oncology (50.7%) and Therapeutic (49%) units.

2) *Klebsiella pneumoniae.* Leading pathogen in MDR is *Klebsiella pneumoniae* (68.91%). It was MDR in 133 cases out of 193 culture-positive isolates. Most isolates came from blood (16) and wound/pus/skin (13) specimens. Out of 16 samples from blood 13 appeared to be MDR. The majority (51) of *Kl. pneumoniae* positive culture are from Oncology unit. Out of 51, 39 (76.4%) are multidrug resistant. In Neonatology ICU 8 out of 9 *Kl. pneumoniae-positive* are MDR, making the researchers pay special attention about the procedures in Neonatology ICU that contribute to the excessive level of multidrug resistance.

3) *Pseudomonas aeruginosa* showed the greatest increase in multidrug resistance from 6.73% in 2015, 10.43% in 2016, 19.59% in 2017. It has resistance to Ceftazidime 44.57%, and relatively high resistance to 4th generation of antibiotics (cefepime, piperacillin). Moreover, least resistance to a complex antibiotic Piperacillin/Tazobactam 11.35% and Norfloxacin (9.52%) and Ciprofloxacin (15.3%). This pathogen is the most common culture positive samples from Pediatric (15.9%) and Surgery (17.9%) units. Out 39 culture-positive samples for *P. aeruginosa*, 14 are multidrug resistant in Surgery Unit. In 55% cases *P. aeruginosa* appeared to be resistant from swabs taken from urine catheters.

4) *Escherichia coli* is the most frequent isolate which possesses MDR 21.73% of all MDR isolates, the majority of samples are from urine in Uronephrology unit. Similar tendency was described in Russia [47]. Multidrug resistant in 141 out of 222 culture positive isolates making 63.5% resistance. Highly resistant to many antibiotics including ampicillin (97.7%), amoxicillin (97.27%), ticarcillin/clavulanate (70.77%). Drugs of choice to treat culture-positive is piperacillin/tazobactam (1.4%), carbapenems (1.5-2.5%). This pattern of resistance has been shown by many studies. [42,43,44,46]

5) *Staphylococcus aureus* is most common isolate from nose (43.1%), but only 8 out of 83 are MDR (9.6%). Isolated from pus/skin/wound 26.3%, but only 3 out 40 are MDR (7.5%). Out of 197 isolated, from the throat 45 are MDR (22.8%). The conclusion is that the *St. aureus* isolated from the throat tend to be more resistant to multiple antibiotics. *St. aureus* comprises 70% of MDR pathogens in Rheumatology unit. *St. aureus* is in a great extent (~90%) resistant to penicillin, ampicillin, amoxicillin, whereas low resistance to erythromycin, gentamycin and azithromycin, making them drugs of choice for treatment.

6*) Staphylococcus epidermidis* comprises 60.24% of all MDR pathogens from blood are positive for *St. epidermidis*. Out of 65 culture-positive samples, 50 are MDR (76.9%). Out of 31 all MDR, 18 contain MDR *St. epidermidis*, making Neonatology Unit a leader (58%) in MDR *St. epidermidis* positive samples. According to logistic regression, Neonatology unit has 27 times more MDR that Rheumatology Unit. Blood samples with MDR St. epidermidis are main contributors to the aforementioned association. The highest resistance to penicillin 97.67% with relatively elevated resistance to many other available antibiotics ranging from 35% to 50% (erythromycin, clarithromycin, azithromycin, trimethoprim/sulfamethoxazole, doxycycline, tetracycline, chloramphenicol). Drugs of choice for treatment with low resistance are gentamycin, vancomycin, linezolid, moxifloxacin).

7) *Acinetobacter baumannii*. Out of 83 culture-positive samples for this pathogen, 29 demonstrated multidrug resistance. The highest prevalence of resistance was noticed from intubation tube swabs. 5 out 6 *A. baumannii* are MDR. More than 1/3 of all MDR *A. baumannii* is from Pediatric ICU. Out of 28 samples with *A.baumannii*, 13 are MDR (46.4%). This pathogen has resistance to third generation of cephalosporins (~35%), the highest resistance to ticarcillin/clavulanate (44.44%), the lowest to amikacin (4.94%).

8) *Enterococcus faecalis* Out of 188 culture-positive, 18 are MDR. Gynecology unit has 36% *E. faecalis* of all culture-positive samples, the good sign is that only one out of 27 is multidrug resistant. Also, there is notable decrease in MDR over time from 5.38% multidrug resistant in 2015, 1.08% in 2016 and 2.03% in 2017. Resistance to ampicillin and amoxicillin ~9%. The greatest prevalence of resistance to norfloxicin (25%) and tetracycline (19.75%). Least prevalence of resistance to vancomycin and linezolid ~5%. This percentage gave us the reason to consider *Ent. faecalis* as relatively easy to choose antibiotic therapy.

9) *Streptococcus pneumoniae*

No MDR was found, according to the criteria of this study to be considered as MDR. The greatest resistance 40% trimethoprim/sulfamethoxazole. The resistance to penicillin is only 12% and less with erythromycin and doxycycline.

10) *Stenotrophomas maltophilia* The sample size of MDR pathogens was 41, but this particular pathogen was included into the study due to high resistance frequency. Out of 109 culture-positive samples, 41 appeared to be MDR. Out of 23 culture-positive for *St. maltophilia*, 13 are MDR in Pediatric ICU. Most samples came from intubation tube swabs, 7 out 11 swabs are MDR. Most resistant to ticarcillin/clavulanate 76.92% and ceftazidime 60%, least resistant to levofloxacin 0% and trimethoprim/sulfomethoxazole 2.5%.

11) *Candida albicans and Candida tropicalis* Out of 208, 27 were MDR *Candida albicans* making this pathogen be multidrug resistance in 13% cases. *Candida tropicalis* was MDR in 20% cases (out of 50 culture-positive, 10 was multidrug resistant). The is a noticeable drop in resistance over time in *Candida albicans* from 8.52% in 2015, 2.52% in 2016 and 0.68 in 2017. Both pathogens are more (15-35%) resistant to imidazoles and triazoles, less (0-1%) resistant to Polyenes (Nystatin, Amphotericin).

Global trends

As with global trends, where *Pseudomonas aeruginosa* showed increase of Multidrug resistance in time according to (37, 38); similar dynamics was obtained from this study.

E.coli showed the greatest prevalence among multidrug resistant pathogens which aligned with global trends (39).

Similar to global trends, ICU units are the epicenters for multidrug resistance in Mother and Child Health Center (40).

Strengths

The sample size of this study was large which allowed us to obtain results with statistical significance without any manipulation. Importantly, large number (n>50.) of important pathogens were isolated. Pathogens were tested for a great number (n=60) of antibiotic sensitivity/resistance.

No similar studies have been published in Kazakhstan at the time of conducting the study

Limitations

This study was conducted only in one hospital. Regrettably, no data whether patients were taking antibiotic before the tests for antibiotic sensitivity were available, since antibiotics are easily available over-the-counter medications. Similarly, no previous history of antibiotic use was available as it is the main factor for antimicrobial resistance development. Relatively short period of time (2.5 years only) during the study was insufficient to show trends that reflect the true scenario. Major inconsistency was found in the dataset during data management and analysis, thus mistakes and errors might be erosive for the reliability of results.

CONCLUSION AND RECOMMENDATIONS

The findings of this study show that there is a need for further research to find reasons and possible measure to combat increased MDR in Neonatology ICU and other hospital units with elevated MDR prevalence. One recommendation is that *Streptococcus mitis* should not be tested extensively for drug resistance, since the majority of results are sensitive to penicillin. There are expenses involved in testing that are not effectively used.

Increase in prevalence of MDR *Pseudomonas aeruginosa* with time need to be closely monitored further. As with the global trends, the MDR prevalence of this pathogen rises, monitoring will help to trace the trend further.

In addition, the necessity to implement central system of gathering and monitoring data of antibiotic/antimicrobial resistance such as CAESAR or GLASS (in Europe or the world respectfully). As working with not standardized data might reveal incorrect or false results.

APPENDIX

Table 1 Distribution of pathogens by Hospital Unit

Distribution of pathogens by Hospital Unit	Culture-positive (n/%)	Multidrug resistant (n/%)
Mother ICU	37/1.26	9/1.39
Neonatology ICU	45/1.53	31/4.78
Pediatric ICU	390/13.48	146/22.5

Uronephrology	389/13.42	132/20.34
Gynecology	75/2.55	12/1.85
Oncology	1140/38.82	182/28.04
Therapeutic unit	511/17.4	78/12.02
Surgery	84/2.86	39/6.01
Rheumatology	266/9.06	20/3.08
Total	**2937/100**	**649/100**

Figure 2 Distribution of culture-positive samples by Hospital Unit

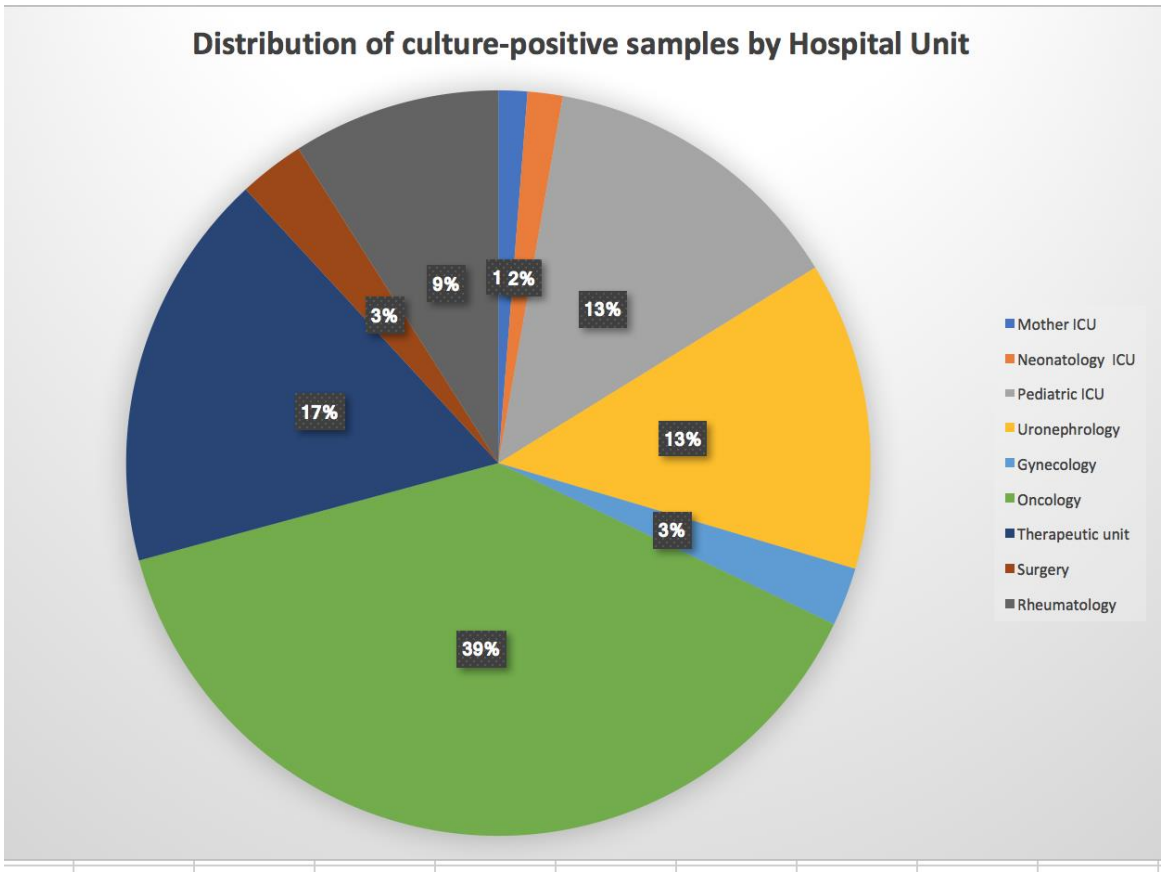

Figure 3 Distribution of multidrug resistant pathogens by Hospital Unit

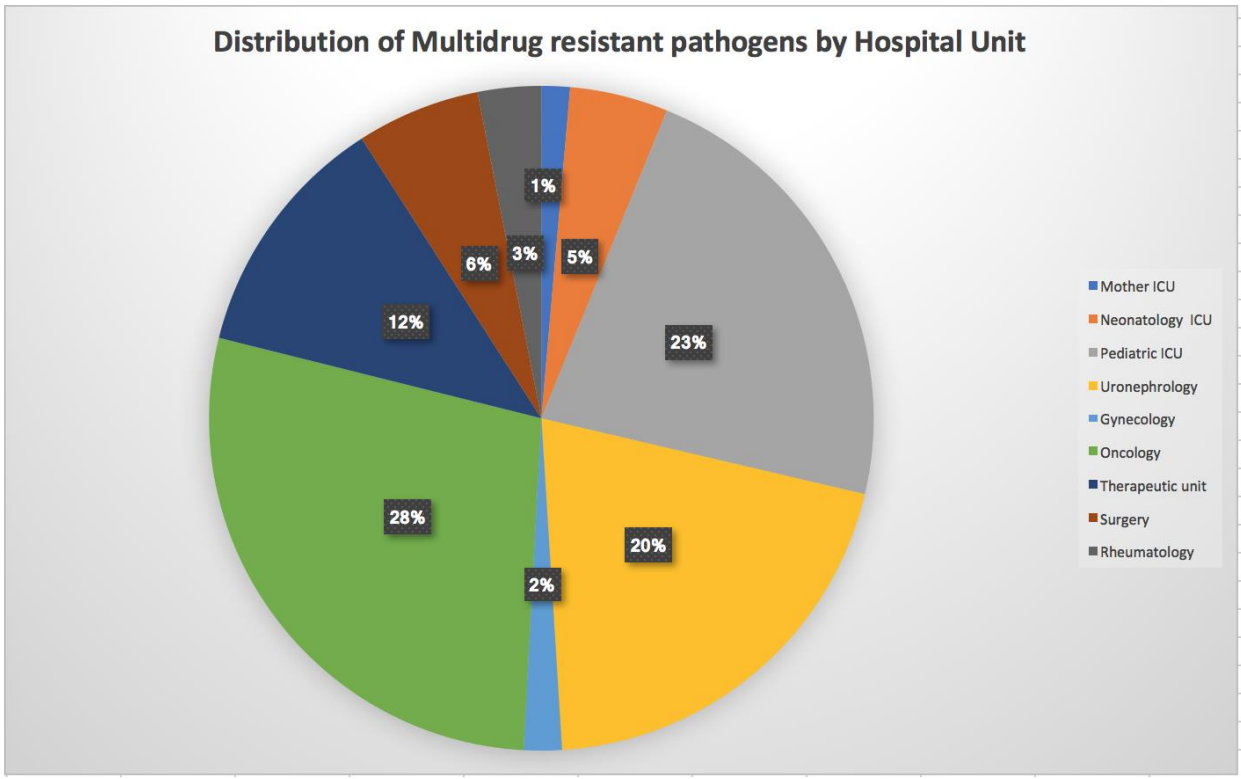

Table 2 Distribution of culture-positive and multidrug resistant pathogens

Distribution of pathogens	Culture-positive (n/%)	Multidrug resistant (n/%)

Acinetobacter baumannii	83/2.83	29/4.47
Candida albicans	208/7.08	274.16
Candida tropicalis	50/1.7	10/1.54
Enterococcus faecalis	188/6.4	18/2.77
Escherichia coli	222/7.56	141/21.73
Klebsiella pneumoniae	193/6.57	133/20.49
Pseudomonas aeruginosa	198/6.74	73/11.25
Staphylococcus aureus	389/13.24	73/11.25
Staphylococcus epidermidis	230/7.83	109/16.8
Stenotrophomonas maltophilia	41/1.4	24/3.7
Streptococcus mitis	1085/36.94	12/1.85

Streptococcus pneumoniae	50/1.7	0/0
Total	**2937/100**	**649/100**

Figure 4 Distribution of culture-positive samples

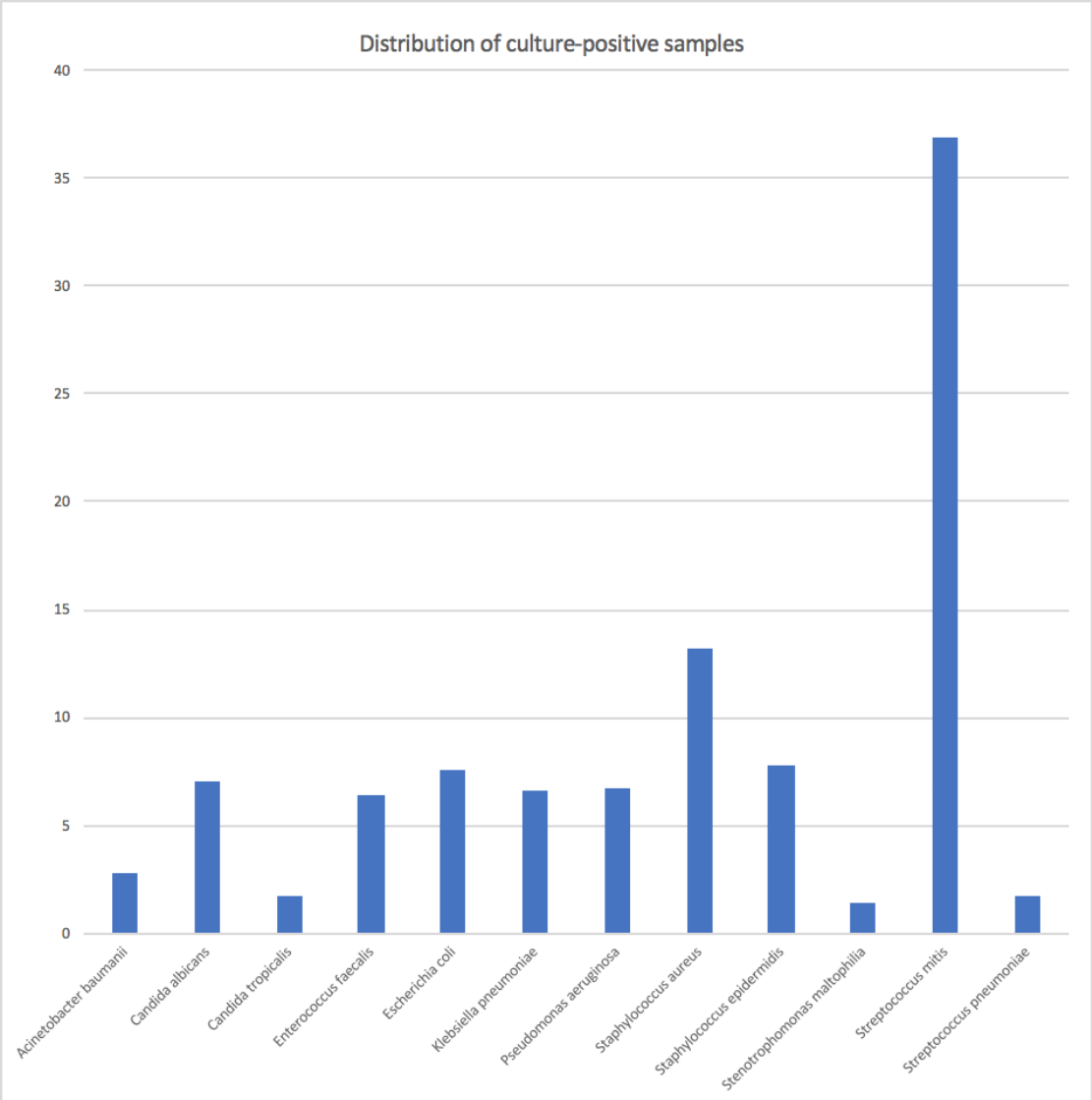

Figure 5 Distribution of multidrug resistant pathogens

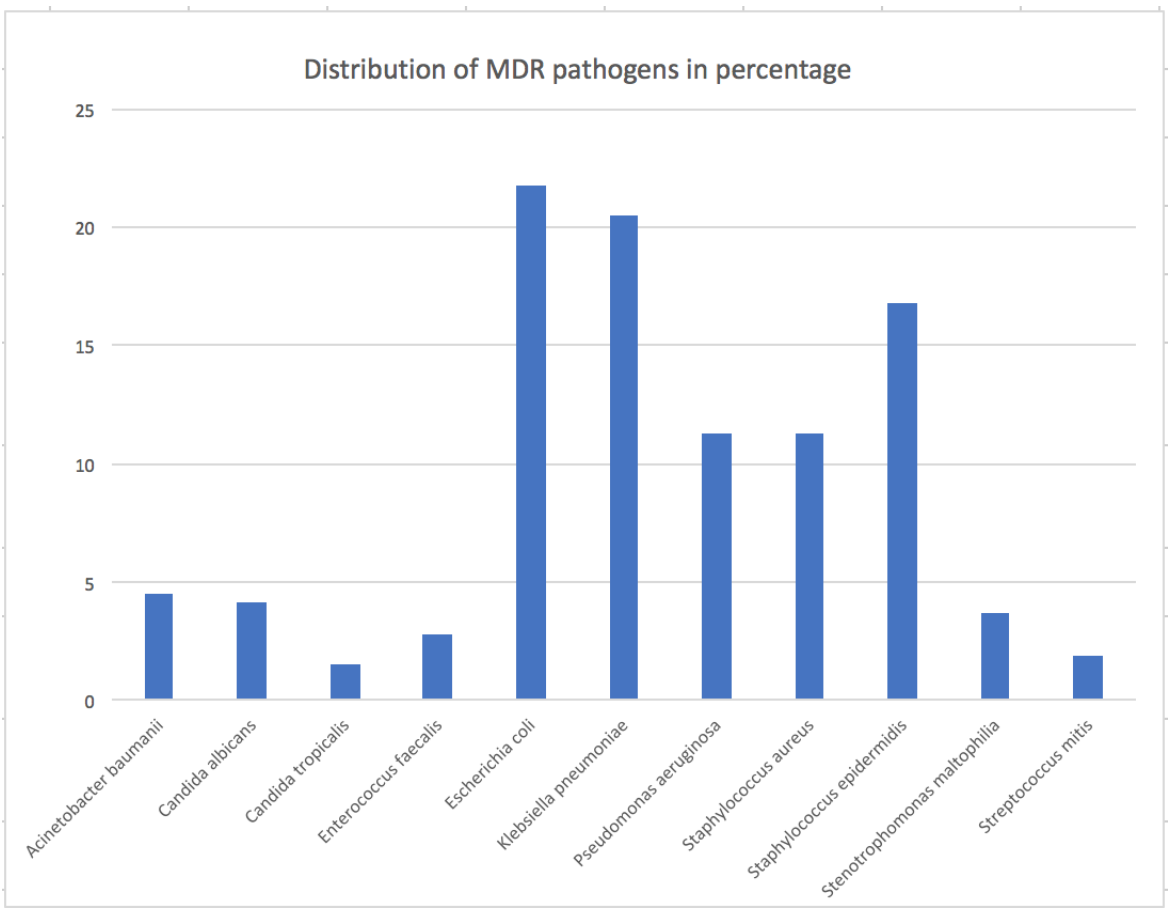

Table 3 Distribution of pathogens by Hospital Unit

Distribution of pathogens by Hospital Unit	Mother ICU	Neonatology ICU	Pediatric ICU	Uronephrology	Gynecology	Oncology	Therapeutic Unit	Rheumatology	Surgery	Total
Acinetobacter baumannii	4	3	28	6	1	30	7	0	4	83
Candida albicans	7	2	44	12	6	65	58	9	5	208
Candida tropicalis	0	0	20	5	2	13	10	0	0	50
Enterococcus faecalis	5	5	37	45	27	47	10	5	7	188
Escherichia coli	10	7	23	93	15	46	10	6	12	222
Klebsiella pneumoniae	3	9	40	44	4	51	22	11	9	193
Pseudomonas aeruginosa	0	3	62	37	0	54	16	11	15	198
Staphylococcus aureus	5	0	27	42	14	135	75	81	10	389
Staphylococcus epidermidis	3	14	40	31	4	97	28	3	10	230
Stenotrophomonas maltophilia	0	0	23	5	0	9	2	0	2	41
Streptococcus pneumoniae	0	0	6	3	0	15	22	4	0	50
Streptococcus	0	2	40	66	2	578	251	136	10	1085

mitis										
Total	37	45	390	389	75	1140	511	266	84	**2937**

Table 4 Distribution of pathogens by Specimen type

Distribution of pathogens by Specimen type	**Culture-positive (n/%)**	**Multidrug-resistant (n/%)**
abdominal cavity	12/0.41	8/1.23
blood	166/5.65	83/12.79
breast milk	2/0.07	1/0.15
cervix	55/1.87	11/1.69
intubation tube	87/2.96	45/6.93
nasogastric tube	22/0.75	11/1.69
nose	197/6.71	44/6.78
pus/wound/skin	152/5.18	51/7.86
sputum	76/2.59	14/2.16
stool	18/0.61	10/1.54

subclavian catheter	53/1.8	27/4.16
throat	1573/53.56	138/21.26
urine	493/16.79	197/30.35
urine catheter	31/1.06	9/1.39
Total	**2937/100**	**649/100**

Table 5 Distribution of culture-positive pathogens by Specimen type

Distribution of culture-positive pathogens by Specimen type	abdominal cavity	blood	breast milk	cervix	intubation tube	nasogastric tube	nose	pus/wound/skin	sputum	stool	subclavian catheter
Acinetobacter baumannii	0	6	1	1	6	4	9	5	6	1	2
Candida albicans	0	10	0	4	7	1	7	4	9	3	1
Candida tropicalis	1	10	0	2	0	0	0	1	1	0	1
Enterococcus faecalis	1	15	0	27	2	1	1	18	1	1	5
Escherichia coli	5	7	0	9	6	2	5	10	2	5	4

Klebsiella pneumoniae	1	16	0	4	9	3	7	13	6	2	9
Pseudomonas aeruginosa	3	17	0	0	24	7	7	13	6	3	1
Staphylococcus aureus	1	9	0	7	10	0	85	40	6	1	7
Staphylococcus epidermidis	0	65	1	1	7	1	52	29	1	1	22
Stenotrophomonas maltophilia	0	4	0	0	11	2	0	5	2	1	1
Streptococcus pneumoniae	0	0	0	0	1	0	8	4	1	0	0
Streptococcus mitis	0	7	0	0	4	1	15	4	31	0	0
Total	**12**	**166**	**2**	**55**	**87**	**22**	**197**	**152**	**76**	**18**	**53**

Table 6 Sample distribution of pathogens by Hospital Unit

Sample distribution of pathogens by Hospital Unit	**Mother ICU**	**Neonatology ICU**	**Pediatric ICU**	**Uroneph rology**	**Gynecology**	**Oncology**	**Therapeutic Unit**	**Rheumatology**	**Surgery**	**Total**
abdominal cavity	0	1	5	0	0	3	0	1	2	12

blood	12	27	41	7	2	48	25	1	13	166
breast milk	1	0	0	0	0	0	0	0	1	2
cervix	1	0	3	0	45	1	3	1	1	55
intubation tube	2	2	56	4	0	21	0	0	2	87
nasogastric tube	0	0	15	2	0	3	1	0	1	22
nose	0	3	46	23	0	118	8	2	7	197
pus/wound/skin	3	3	26	5	6	71	20	4	14	152
sputum	4	1	17	11	1	10	26	4	2	76
stool	0	1	12	2	0	2	0	0	1	18
subclavian catheter	2	2	14	0	0	29	6	0	0	53
throat	0	4	92	77	3	748	387	246	16	1573
urine	22	0	52	252	18	86	33	7	23	493
urine catheter	0	1	21	6	0	0	2	0	1	31
Total	37	45	390	389	75	1140	511	266	84	**2937**

Table 7 Distribution of multidrug resistant pathogens by Hospital Unit

Distribution of multidrug pathogens by	Mother ICU	Neonatology	Pediatric ICU	Uronephrology	Gynecology	Oncology	Therapeutic	Rheumatology	Surgery	Total

Hospital Unit	ICU		ogy				Unit	gy		
Acinetobacter baumannii	2	3	13	2	0	7	1	0	1	29
Candida albicans	0	0	7	0	0	6	12	2	0	27
Candida tropicalis	0	0	6	1	1	1	1	0	0	10
Enterococcus faecalis	1	0	2	4	1	8	1	0	1	18
Escherichia coli	3	7	16	64	4	32	4	3	8	141
Klebsiella pneumoniae	1	8	33	29	1	39	13	0	9	133
Pseudomonas aeruginosa	0	2	25	13	0	16	3	0	14	73
Staphylococcus aureus	1	0	7	7	2	23	19	14	0	73
Staphylococcus epidermidis	1	11	24	7	3	40	17	1	5	109
Stenotrophomonas maltophilia	0	0	13	4	0	5	1	0	1	24
Streptococcus pneumoniae	0	0	0	0	0	0	0	0	0	0
Streptococcus	0	0	0	1	0	5	6	0	0	12

mitis										
Total	**9**	**31**	**146**	**132**	**12**	**182**	**78**	**20**	**39**	**649**

Table 8 Distribution of multidrug resistant pathogens by Specimen type

Distribution of multidrug resistant pathogens by Specimen type	**abdominal cavity**	**blood**	**breast milk**	**cervix**	**intubation tube**	**nasogastric tube**	**nose**	**pus/wound/skin**	**sputum**	**stool**	**subclavian catheter**
Acinetobacter baumannii	0	3	0	0	5	1	4	2	2	0	1
Candida albicans	0	1	0	0	1	0	0	0	2	1	0
Candida tropicalis	0	0	0	1	0	0	0	1	0	0	0
Enterococcus faecalis	0	0	0	3	0	1	0	1	0	0	1
Escherichia coli	3	6	0	3	3	2	4	7	1	3	4
Klebsiella pneumoniae	1	13	0	3	8	3	5	11	3	2	9
Pseudomonas aeruginosa	3	6	0	0	15	2	3	11	4	2	0
Staphylococcus aureus	1	2	0	0	2	0	8	3	0	0	3

Staphylococcus epidermidis	0	50	1	1	4	0	20	12	0	1	8
Stenotrophomonas maltophilia	0	2	0	0	7	2	0	2	2	1	1
Streptococcus pneumoniae	0	0	0	0	0	0	0	0	0	0	0
Streptococcus mitis	0	0	0	0	0	0	0	1	0	0	0
Total	**8**	**83**	**1**	**11**	**45**	**11**	**44**	**51**	**14**	**10**	**27**

Table 9 Sample distribution of multidrug resistant pathogens by Hospital Unit

Sample distribution of multidrug pathogens by Hospital Unit	**Mother ICU**	**Neonatology ICU**	**Pediatric ICU**	**Uroneph rology**	**Gynecology**	**Oncology**	**Therapeutic Unit**	**Rheumatology**	**Surgery**	**Total**
abdominal cavity	0	1	5	0	0	3	0	1	2	12
blood	12	27	41	7	2	48	25	1	13	166
breast milk	1	0	0	0	0	0	0	0	1	2
cervix	1	0	3	0	45	1	3	1	1	55
intubation	2	2	56	4	0	21	0	0	2	87

tube										
nasogastric tube	0	0	15	2	0	3	1	0	1	22
nose	0	3	46	23	0	118	8	2	7	197
pus/wound/skin	3	3	26	5	6	71	20	4	14	152
sputum	4	1	17	11	1	10	26	4	2	76
stool	0	1	12	2	0	2	0	0	1	18
subclavian catheter	2	2	14	0	0	29	6	0	0	53
throat	0	4	92	77	3	748	387	246	16	1573
urine	22	0	52	252	18	86	33	7	23	493
urine catheter	0	1	21	6	0	0	2	0	1	31
Total	**37**	**45**	**390**	**389**	**75**	**1140**	**511**	**266**	**84**	**2937**

Table 10 Resistance frequency of Gram-negative pathogens

Resistance frequency of Gram -negative pathogens (n/% of multidrug resistant)	***Acinetobacter baumannii***	***Escherichia coli***	***Klebsiella pneumoniae***	***Pseudomonas aeruginosa***	***Stenotrophomas maltophilia***
Ampicillin		220/97.70	194/99.48		

Cefazolin		215/61.86	190/77.37		
Gentamycin	82/17.07	217/9.22	190/28.42	188/34.57	
Amoxicillin		110/97.27	104/100		
Ceftazidime	82/31.71			184/44.57	40/60.00
Piperacillin		147/66.67	148/75.68	173/32.95	
Trimetoprim/sulfametoxazol	79/37.97				40/2.50
Doxycycline	82/15.85				
Tetracycline	81/16.05				
Piperacillin/Tazobactam	84/11.90	211/1.40	189/4.76	185/11.35	
Piperacillin	42/28.57				
Amoxicillin/Clavulanate		201/71.14	187/82.35		
Ampicillin/Sulbactam	77/33.77	192/64.58	184/76.09		
Cefepime	82/29.27	207/34.30	191/53.40	192/32.81	
Cefotaxime	82/35.37	200/37.50	190/56.84		

Meropenem	83/13.25	195/2.56	187/5.88	181/16.02	
Ceftriaxone	82/36.59	196/38.27	184/56.52		
Ertapenem		168/1.79			
Aztreonam				179/25.70	
Amikacin	81/4.94	200/0.50	186/6.99	178/19.10	
Imipenem	82/13.41	198/2.53	183/5.46	183/21.86	
Ciprofloxacin	83/13.25	197/14.72	184/9.24	183/15.30	
Cefuroxime		197/50.25	183/68.85		
Ticarcillin/Clav	81/44.44	195/70.77	178/83.15		39/76.92
Levofloxacin	81/12.35	196/10.71	187/7.49	183/14.21	39/0.00
Lomefloxacin		93/23.66			
Tobramycin	26/11.54				
Nitrofurantoin		71/4.23			
Minocycline	27/11.12				
Norfloxacin		84/14.29		42/9.52	
Trimetoprim		84/66.67			
Chrloramfenicol					40/15.0

				0
Ofloxacin		96/20.83	45/11.11	

Table 11 Resistance frequency of Gram-positive pathogens

Resistance frequency of Gram-positive pathogens (n/% of multidrug resistant)	***Enterococcus faecalis***	***Staphylococcus aureus***	***Streptococcus epidermidis***	***Streptococcus mitis***	***Streptococcus pneumoniae***
Erithromycin		357/9.52	190/50.00		50/2.00
Penicillin	180/18.33	385/97.40	215/97.67	1061/4.24	50/12.00
Oxacillin		386/5.70	214/21.49		
Clarithromycin		357/8.40	189/48.67		
Ampicillin	183/8.74	31/87.09		1068/1.22	
Gentamycin		61/6.57	96/11.46		
Azithromycin		359/8.65	190/48.42		
Amoxicillin	52/9.62	30/90.00		1063/0.47	
Clindamycin		337/3.56	183/23.50		46/6.52
Trimetoprim/sulfametoxazol		381/6.04	213/48.35		50/40.00
Vancomycin	182/0.55	387/0.00	216/0.93	1065/0.00	50/0.00
Doxycycline		374/12.8	193/35.75		

		3			
Tetracycline	81/19.75	386/12.95	211/33.18		50/4.00
Linezolid	177/0.56	384/0.00	212/0.94		
Cefepime				1040/0.87	49/0.00
Cefotaxime				1045/0.67	48/0.00
Meropenem					49/0.00
Ceftriaxone				1041/0.67	49/0.00
Ciprofloxacin	91/12.09	78/6.41	112/19.64		
Levofloxacin	91/5.49	78/5.13	112/11.61		50/0.00
Moxifloxacin		74/1.35	104/2.88		49/0.00
Nitrofurantoin	44/2.27				
Norfloxacin	72/25.00				
Chrloramfenicol		67/11.94	110/35.45		
Ofloxacin		52/5.77	83/18.07		47/0.00

Table 12 Fungi multidrug resistance frequency

Fungi resistance frequency (n/% of multidrug resistant)	***Candida albicans***	***Candida tropicalis***

Itraconazole	156/13.46	37/21.62
Fluconazole	201/29.85	46/32.61
Nystatin	203/0.00	47/0.00
Clotrimazole	202/16.34	47/23.40
Ketoconazole	201/21.89	46/21.74
Amphotericin	177/1.13	43/11.63

Table 13 Contingency table of age groups and their distribution

	Contingency table by age group		
	Cases	**Controls**	
0-5 years	265 *272.45* (0.20)	969 *961.55* (0.06)	**1234**
5-12 years	195 *173.09* (2.77)	589 *610.91* (0.79)	**784**
12-18 years	92 *98.47* (0.43)	354 *347.53* (0.12)	**446**
> 18 years	96 *103.99* (0.61)	375 *367.01* (0.17)	**471**
	648	**2287**	**2935**

χ^2 = 5.152, df = 3, χ^2/df = 1.72 , P(χ^2 > 5.152) = 0.1610

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