Stratification of cumulative antibiograms in hospitals for hospital unit, specimen type, isolate sequence and duration of hospital stay

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Abstract

Background Empirical antibiotic therapy is based on patients' characteristics and antimicrobial susceptibility data. Hospital-wide cumulative antibiograms may not sufficiently support informed decision-making for optimal treatment of hospitalized patients. Methods We studied different approaches to analysing antimicrobial susceptibility rates (SRs) of all diagnostic bacterial isolates collected from patients hospitalized between July 2005 and June 2007 at the University Hospital in Zurich, Switzerland. We compared stratification for unit-specific, specimen type-specific (blood, urinary, respiratory versus all specimens) and isolate sequence-specific (first, follow-up versus all isolates) data with hospital-wide cumulative antibiograms, and studied changes of mean SR during the course of hospitalization. Results A total of 16 281 isolates (7965 first, 1201 follow-up and 7115 repeat isolates) were tested. We found relevant differences in SRs across different hospital departments. Mean SRs of Escherichia coli to ciprofloxacin ranged between 64.5% and 95.1% in various departments, and mean SRs of Pseudomonas aeruginosa to imipenem and meropenem ranged from 54.2% to 100% and 80.4% to 100%, respectively. Compared with hospital cumulative antibiograms, lower SRs were observed in intensive care unit specimens, follow-up isolates and isolates causing nosocomial infections (except for Staphylococcus aureus). Decreasing SRs were observed in first isolates of coagulase-negative staphylococci with increasing interval between hospital admission and specimen collection. Isolates from different anatomical sites showed variations in SRs. Conclusions We recommend the reporting of unit-specific rather than hospital-wide cumulative antibiograms. Decreasing antimicrobial susceptibility during hospitalization and variations in SRs in isolates from different anatomical sites should be taken into account when selecting empirical antibiotic treatment.
Stratification of Cumulative Antibiograms in Hospitals for Hospital Unit, Specimen Type, Isolate Sequence and Duration of Hospital Stay

Stefan P. Kuster¹, Christian Ruef¹, Reinhard Zbinden², Jochen Gottschalk², Bruno Ledergerber¹, Lutz Neuber³, Rainer Weber*¹

¹Division of Infectious Diseases and Hospital Epidemiology, University Hospital, Zurich, Switzerland
²Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland
³SAP Customer Competence Center, University Hospital, Zurich, Switzerland

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Running head: Analyses of cumulative antibiograms

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*Correspondence to:
Rainer Weber, MD
Division of Infectious Diseases and Hospital Epidemiology
University Hospital Zurich
Raemistrasse 100
CH-8091 Zurich, Switzerland
Tel +41 44 255 2541, Fax +41 44 255 3291
Email: rainer.weber@usz.ch
ABSTRACT (250 words)

Background: Empirical antibiotic therapy is based on patients' characteristics and antimicrobial susceptibility data. Hospital-wide cumulative antibiograms may not sufficiently support informed decision making for optimal treatment of hospitalized patients.

Methods: We studied different approaches in analyzing antimicrobial susceptibility rates (SR) of all diagnostic bacterial isolates collected from patients hospitalized between July 2005 and June 2007 at the University Hospital in Zurich, Switzerland. We compared stratification for unit-specific; specimen type-specific (blood, urinary, respiratory versus all specimens); and isolate sequence-specific (first, follow-up versus all isolates) data with hospital-wide cumulative antibiograms; and studied changes of mean SR during the course of hospitalization.

Results: A total of 16,281 isolates (7,965 first, 1,201 follow-up and 7,115 repeat isolates) were tested. We found relevant differences in SR across different hospital departments. Mean SR of \textit{Escherichia coli} to ciprofloxacin ranged between 64.5 and 95.1\% in various departments, and mean SR of \textit{Pseudomonas aeruginosa} to imipenem and meropenem ranged from 54.2 to 100\% and 80.4 to 100\%, respectively. Compared with hospital cumulative antibiograms, lower SR were observed in intensive care unit specimens, follow-up isolates and isolates causing nosocomial infections (except for \textit{Staphylococcus aureus}). Decreasing SR were observed in first isolates of coagulase-negative staphylococci with increasing interval between hospital admission and specimen collection. Isolates from different anatomic sites showed variations in SR.

Conclusions: We recommend to report unit-specific rather than hospital-wide cumulative antibiograms. Decreasing antimicrobial susceptibility during
hospitalization and variations in susceptibility rates in isolates from different anatomic sites should be taken into account when selecting empirical antibiotic treatment.
INTRODUCTION

Antibiotic resistance rates vary widely between countries,\textsuperscript{1-3} within countries,\textsuperscript{4} and between as well as within health care institutions.\textsuperscript{5} The worldwide emergence of antibiotic resistance due to increased and inappropriate antibiotic use reduces treatment options and the overall efficacy of antimicrobials.\textsuperscript{2, 6} In patients with presumed acute infection, initial empirical antibiotic therapy - before results of pathogen identification and susceptibility testing are available - is selected based on individual patient's characteristics, clinical differential diagnosis, place of infection (i.e., community versus hospital-acquired), and non-patient-related epidemiological data such as local bacterial susceptibility rates.\textsuperscript{5, 7} The choice of empirical antibacterial therapy in hospitalized patients is guided by institution-specific cumulative antibiogram reports, which compile mean susceptibility rates of bacterial isolates collected from other patients previously treated at the same institution.

Guidelines for the analysis and preparation of cumulative antibiograms in hospitals have recently been updated.\textsuperscript{8} They recommend to only include the first isolate per episode of a patient's infection in order to reduce potential overestimation of antimicrobial resistance due to multiple specimens from the same patient. However, it may not be adequate to base empirical antibiotic therapy for individual patients on hospital-wide overall susceptibility rates.\textsuperscript{5} Incorrect initial empirical treatment may affect outcome, particularly in critically ill patients.\textsuperscript{9, 10}

In order to support guidelines for empirical antibiotic therapy at our institution, we aimed to compare the hospital-wide cumulative antibiograms of inpatients with the results of additional subanalyses of susceptibility data. In particular, we stratified hospital unit-specific versus hospital-wide susceptibility rates; anatomic site-specific (blood, urinary, respiratory versus all specimens); isolate sequence-specific (first,
follow-up versus all isolates); and hospitalization phase-specific (considering the time between admission and specimen collection) susceptibility data.
MATERIALS AND METHODS

Setting

The University Hospital in Zurich, Switzerland, is an 860 beds tertiary care teaching hospital. It covers all medical specialties except for paediatrics and orthopaedics. Six intensive care units (medical ICU, general, thoracic and transplant surgery ICU, trauma ICU, burn ICU, cardiac surgery ICU, neurosurgery ICU) with a total of 59 beds are assigned to different departments. Bone marrow transplantations are performed in a specialized unit.

Data collection

Antimicrobial susceptibility rates were assessed and recorded during routine clinical patient care for all diagnostic bacterial isolates obtained from inpatients hospitalized in intensive care units and general wards between July 1, 2005 and June 30, 2007, and were analyzed retrospectively. For comparisons of nosocomial and community-acquired isolates, isolates from patients spending >24 hours in the emergency unit, its observation ward or surgical observation wards were also included. Screening isolates (e.g. samples that were analyzed at our Hospital Epidemiology Department in order to assess the need for ongoing isolation measures in patients who had previously been identified as carriers of methicillin-resistant Staphylococcus aureus and Extended-Spectrum Beta-Lactamase producing Enterobacteriaceae) were excluded. All specimens were tested in a central clinical microbiology laboratory (Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland). Bacteria were isolated from blood cultures and other materials according to standard methods. Susceptibility testing of bacterial isolates was performed by the disk diffusion method; zone diameters were interpreted according
to the NCCLS (CLSI) guidelines. Intermediate susceptibility was categorized as non-susceptible.

The isolates were categorized by the patient’s unit of hospitalization at the time of specimen collection; the anatomic site of specimen recovery (blood culture, urinary, respiratory or other); and the year of collection. Unless specified otherwise, susceptibility rates of first isolates are reported according to the recently published Clinical Laboratory Standards Institute (CLSI) guidelines. The problem of handling different phenotypes with different resistance patterns of an isolate has not been addressed in these guidelines. Hence, we counted one organism if an isolate revealed two or more phenotypes of the same organism. However, we included all phenotypes if they showed different resistance patterns. As a result, the number of susceptibility testing results exceeds the total number of organisms. Recovery of a minimum of 30 isolates per each hospital unit or anatomic site of infection was required to be included in the analysis, as recommended.

Among the repeat isolates, we analyzed the first follow-up isolates in two groups, which were a priori defined, i.e., ‘early’ follow-up isolates collected between day 0 and 2 after the first isolate, and ‘late’ follow-up isolates collected more than 2 and equal or less than 10 days after the first isolate.

Nosocomial isolates were defined as isolates that were collected more than 48 hours after hospital admission and less than 30 days after discharge (in case of readmission) or, in case of missing date of specimen collection, if they arrived at the Institute of Medical Microbiology more than 72 hours after hospital admission.

Respiratory isolates were defined as isolates recovered from tracheal aspirates, bronchial aspirates or broncho-alveolar lavage. No assessments against other confounders were made when analyzing data on pathogen susceptibility from different anatomic locations.
Antimicrobial susceptibility rates of all bacterial isolates were determined, but we limit our report to the analyses of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and coagulase-negative staphylococci, as these organisms were isolated most frequently, accounting for 28% of all first isolates.

### Statistical analyses

We used Stata (Version 9.2, StataCorp, College Station, Texas) for statistical analyses. Fisher's exact test was used in the analysis of categorical data. Exact 95% confidence intervals for binomial variables were calculated. No adjustments for multiple testing were made. A two-tailed *p* value of less than 0.05 was considered to be statistically significant.
RESULTS

A total of 16,281 diagnostic bacterial isolates from hospitalized patients were tested during the 2-year study period. Among these, 7,965 were first, 1,201 were follow-up isolates (according to our definition) and 7,115 were other repeat isolates.

Unit-specific versus hospital-wide cumulative antibiograms

Table 1 displays the range of hospital-unit-specific susceptibility rates, i.e. the mean rates of the unit with the lowest and the unit with the highest susceptibility rate, in comparison with the mean hospital-wide cumulative susceptibility rate of first isolates of *E. coli*, *P. aeruginosa*, *S. aureus* and coagulase-negative staphylococci.

Figure 1 depicts mean susceptibility rates of *E. coli* in each single ICU and ward.

We detected significant differences in the overall susceptibility rates of *E. coli* and *P. aeruginosa* between departments, i.e., for *E. coli* tested against ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, ciprofloxacin and trimethoprim/sulfamethoxazole; for *P. aeruginosa* tested against ceftriaxone, imipenem, meropenem, piperacillin/tazobactam and tetracycline; and for coagulase-negative staphylococci tested against ampicillin, oxacillin, aminoglycosides, trimethoprim/sulfamethoxazole, ciprofloxacin, erythromycin, clindamycin and rifampicin. For *S. aureus* isolates, significant differences across departments were only detected for penicillin resistance rates.

The most striking and clinically relevant variations in susceptibility rates between departments were:

- mean *E. coli* susceptibility rate to amoxicillin/clavulanic acid, ranging from 62.5 (thoracic and transplant surgery ICU) to 92.7% (department of neurosurgery);
- mean *E. coli* susceptibility rate to ciprofloxacin, ranging from 64.5 (department of dermatology) to 95.1% (department of neurosurgery);
- Mean *E. coli* susceptibility rate to trimethoprim/sulfmethoxazole, ranging from 58.1% (department of rheumatology) to 86.1% (department of neurology);

- Mean *P. aeruginosa* susceptibility rate to piperacillin/tazobactam, ranging from 85.0% (medical ICU) to 100% (departments of dermatology and gynecology and obstetrics);

- Mean *P. aeruginosa* susceptibility rate to imipenem and meropenem, ranging from 54.2% (thoracic and transplant surgery ICU) to 100% (department of gynecology and obstetrics) and from 80.4% (thoracic and transplant surgery ICU) to 100% (department of gynecology and obstetrics), respectively; and

- Mean *P. aeruginosa* susceptibility rate to ciprofloxacin, ranging from 80.0% (medical ICU) to 95.2% (trauma ICU).

**ICUs versus general wards**

Figure 2 contrasts the susceptibility rates of first isolates of *E. coli* and *P. aeruginosa* recovered from intensive care units (*E. coli*, n=333, *P. aeruginosa*, n=290) and general wards (*E. coli*, n=993, *P. aeruginosa*, n=277). The proportion of isolates of *P. aeruginosa* susceptible to imipenem (SR, 67.97% and 90.14%, respectively, p<0.001) and meropenem (SR, 89.56% and 95.67%, respectively, p=0.004) was significantly lower in ICUs than in general wards. In contrast, general wards had significantly higher rates of ciprofloxacin-resistant *E. coli* than ICUs (SR, 81.64% and 90.39%, respectively, p<0.001).

**First versus follow-up versus all isolates**

Figure 3 compares the cumulative antibiograms of first versus follow-up isolates obtained between days 0-2 and 3-10 after the first isolate, respectively, versus all isolates of *E. coli* and *P. aeruginosa*. 
First isolates of \textit{E. coli} (n=1,326) and \textit{P. aeruginosa} (n=567) were significantly more susceptible to various antibiotics than follow-up isolates (\textit{E. coli}, n=221 (‘early’ follow-up isolates) and n=180 (‘late’ follow-up isolates), respectively; \textit{P. aeruginosa}, n=163 (‘early’ follow-up isolates) and n=165 (‘late’ follow-up isolates), respectively) or all isolates (\textit{E. coli}, n=2,491, \textit{P. aeruginosa}, n=1,768). Except for the susceptibility rate of \textit{E. coli} tested to ampicillin (SR, 30.98% (‘late’ follow-up isolates) and 40.97% (all isolates), respectively, p=0.013), no significant differences in susceptibility rates were detected between ‘late’ follow-up and all isolates.

\textbf{Community-acquired versus nosocomial isolates}

Differences between community-acquired and nosocomial isolates are shown in table 2. Community-acquired isolates of \textit{E. coli}, \textit{P. aeruginosa} and of coagulase-negative staphylococci were significantly more often susceptible against various antibiotics than nosocomial isolates. No significant differences between nosocomial and community-acquired isolates regarding antibiotic susceptibility were observed with \textit{S. aureus}.

\textbf{Changes of cumulative antibiograms during the course of hospitalization}

We considered the interval between hospital admission and the collection of a first specimen and calculated cumulative antibiograms of these first isolates for different phases of hospital stay (Figure 4). A sustained and significant decrease in susceptibility rates during the course of hospitalization could be observed in coagulase-negative staphylococci tested against gentamicin, oxacillin and rifampicin, but not in \textit{E. coli} tested against ciprofloxacin, ceftriaxone, amoxicillin/clavulanic acid or piperacillin/tazobactam. Data on changes of susceptibility rates of \textit{P. aeruginosa}

could not be completely obtained due to low numbers of first isolates in some of the
time periods that were assessed.

**Blood, urine or respiratory tract isolates versus all first isolates**

We found significant differences in susceptibility rates of organisms recovered
from different anatomic sites (Figure 5). For example, respiratory isolates of *E.coli*
(n=114) were significantly more often susceptible to ciprofloxacin than first *E.coli*
isolates overall (n=1,768) (SR, 92.11% and 83.83%, respectively, p<0.001). The
susceptibility rate to trimethoprim/sulfamethoxazole of *E.coli* isolates recovered from
blood cultures (n=94) was significantly lower than the respective overall susceptibility
rate (SR, 50.00% and 70.20%, respectively, p<0.001). Furthermore, the proportion of
urinary isolates of *P. aeruginosa* (n=107) with susceptibility to imipenem (SR, 88.89%
and 78.62%, respectively, p=0.012), meropenem (SR, 98.02% and 92.51%,
respectively, p=0.049) and ceftazidime (SR, 99.05% and 93.40%, respectively,
p=0.020) was higher than the corresponding susceptibility rate of all isolates (n=567),
whereas isolates from respiratory specimens (n=190) were more often resistant to
imipenem (SR, 64.10% and 78.62%, respectively, p<0.001).
DISCUSSION

Information from cumulative antibiogram reports is an important basis for the selection of empirical antibacterial therapy. Using stratified analyses of the bacterial susceptibility test results at our hospital, we found clinically highly relevant dissimilarities of susceptibility rates of important bacterial pathogens across various hospital departments, and between intensive care units and general wards. Furthermore, follow-up isolates (identified between more than 48 hours and 10 days after the first isolate) of a variety of bacterial species were less susceptible than first isolates. Likewise, increased duration between hospital admission and specimen collection was associated with reduced antimicrobial susceptibility rates of some bacterial species. Finally, isolates from different anatomic sites differed in their susceptibility rates.

Susceptibility rates of bacterial isolates from certain departments may differ from those of a hospital overall, as previously shown, but comprehensive data on unit-specific data are scarce in the literature. We found striking differences of cumulative antibiograms across different departments of our hospital. For example, mean susceptibility rates of *Escherichia coli* to ciprofloxacin ranged between 64.5 and 95.1%; and those of *Pseudomonas aeruginosa* to imipenem and meropenem ranged from 54.2 to 100% and 80.4 to 100%, respectively. Furthermore, the results of our study are in agreement with findings of previous studies reporting differences in the prevalence of antimicrobial resistance among various pathogens between intensive care units (ICUs), non-ICU units, overall hospital data, and between different ICUs of a single institution.

Calculations of cumulative antibiograms based on all isolates tend to overestimate resistance rates due to repeat collection of strains from patients with complicated clinical course, long hospital stay, or with nosocomial infections. Also, specimen-
collection practices, i.e. the frequency of repeat cultures during patients' evaluation or
the use of surveillance cultures in ICUs, may influence susceptibility rates. Therefore,
guidelines to prepare cumulative antibiogram reports recommend to exclude repeat
isolates per episode, and emphasize that the "first isolate per patient approach" had
direct relevance to guiding selection of initial empirical therapy. In contrast, the
likelihood of the emergence of antimicrobial resistance during prolonged or repeat
therapy has to be taken into account during management of prolonged or re-
occuring infections.

There is no consensus on the definition of a new infectious episode following a
first one in an individual patient, and there are no recommended calculation
algorithms to detect such consecutive infectious episodes by analyzing
microbiological laboratory data sets. However, the "first isolate approach" may
underestimate the resistance rate of complicated infections because first isolates are
often collected early in the course of a disease. Therefore, the knowledge of the
resistance rates of follow-up isolates may help to empirically adjust antibiotic therapy
in patients whose clinical condition is deteriorating despite presumably adequate
initial antibiotic coverage. In order to explore susceptibility data in complicated
infections, we investigated a definition for 'late' follow-up isolates (i.e., isolate
identification between more than 48 hours and 10 days after the first one) which is
expected to exclude most duplicate isolates. We found that, in general, mean
susceptibility rates of 'late' follow-up isolates were lower than first isolates at our
institution. However, we also observed that resistance rates of 'late' follow-up isolates
were similar to the mean of all isolates. Consequently, the easily computable "all
isolate approach" may reflect the resistance pattern of more complicated infection
and may serve as an important information in addition to the first isolate
antibiograms.
Isolates from nosocomial infections are generally regarded less susceptible to antibiotics than community-acquired organisms, but this is not true for all bacteria or for all hospital sites and geographic areas. Nosocomial infection is usually considered if it begins more than 48 h after hospital admission. Nonetheless, the point in time during the course of a hospitalization that best discriminates between more susceptible and more resistant pathogens remains unclear. To our knowledge, there are no data available regarding the influence of the time between hospital admission and specimen collection on cumulative antibiograms. The effects of antibiotic use on resistance rates in hospitals have been described previously. We observed that mean susceptibility rates of coagulase-negative staphylococci for gentamicin, oxacillin and rifampicin continuously and significantly decreased in the course of hospitalization, reflecting the overall selection pressure of antibiotic use in an institution. In contrast, no significant or sustained decrease of susceptibility was detected for *E. coli*, *P. aeruginosa* and *S. aureus*. Of note, the rate of methicillin-resistant *S. aureus* (MRSA) at our institution and in the surrounding region is with approx. 3% exceptionally low. However, as no typing work was done, it remains unclear whether modifications of the primary pathogen or hospital acquisition of different strains have a greater influence on these results. Nevertheless, these findings indicate that a duration of hospitalization of more than 48 h before diagnosis of infection and initiation of empirical antibacterial therapy may not by itself be a sufficient criterion for the use of broad-spectrum antibiotic or MRSA-covering substances.

Whether the anatomic site of specimen collection should be accounted for in cumulative antibiograms is unclear. Analyses comparing resistance rates in isolates from different body sites or blood revealed conflicting results, and only few data on systematic evaluations are available. We found variations in susceptibility rates...
between specimens of different sources, but these differences were small for most
drug-organism combinations. Nevertheless, we observed some significant
discrepancies such as increased carbapenem resistance in many respiratory *P. aeruginosa*
isolates, or an increased resistance rate in uropathogens.

Limitations of the calculation of cumulative antibiograms have been recognized.
Because laboratory data sets are based on the resistance profiles of all isolates sent
to the microbiology laboratory, infection and colonization cannot be distinguished. A
patient's localization in the hospital at the time of sample collection may not represent
the site where infection was acquired. Furthermore, even though screening samples
for surveillance purposes are usually marked, some screening isolates might have
been included in our analyses. We cannot exclude that we found some differences
which could be chance findings due to multiple testing.

In conclusion, we found significant and clinically relevant discrepancies of mean
antimicrobial susceptibility patterns at our institution depending on the strategy used
for data analyses of cumulative antibiograms. From a practical standpoint, data
reporting including multiple stratification may not appear feasible at present, but the
knowledge of variations of susceptibility rates, specifically within an institution, during
different phases of hospitalization, or of infections at different anatomic sites, may
particularly be beneficial for empirical antibiotic therapy of complicated infections. In
the future, electronic decision support systems may integrate the results of stratified
cumulative antibiograms. We recommend the reporting of unit-specific cumulative
antibiograms, although prospective studies are needed to evaluate the impact of
such reporting on antibiotic use, treatment outcome and costs. Furthermore, teaching
antibiotic policies and visualization of the antibiotic selection pressure within the own
institution may be supported by depicting institution-specific data of selected
examples of frequent bacterial isolates with decreasing susceptibility rates during the course of hospitalization.
FUNDING
This study has been funded by the Division of Infectious Diseases and Hospital Epidemiology, University Hospital, Zurich, Switzerland.

TRANSPARENCY DECLARATIONS
S.P.K. has received travel grants from Tibotec. C.R. has received travel grants from Pfizer and Wyeth and honoraria for teaching from Merck Sharp & Dohme and is a member of the advisory board of Pfizer and Novartis. B.L. has received travel grants and honoraria from Abbott, Aventis, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, Roche and Tibotec. R.W. has received travel grants and honoraria for teaching from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Pfizer, Roche and TRB Chemedica. R.Z., J.G. and L.N.: None to declare.
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**Table 1:** Hospital-wide antibiograms and range of unit-specific susceptibility rates of the departments with the lowest and the highest rates.

<table>
<thead>
<tr>
<th></th>
<th>Mean susceptibility rates (% of isolates)</th>
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<tbody>
<tr>
<td></td>
<td>Escherichia coli (n=1,326)</td>
</tr>
<tr>
<td></td>
<td>hospital-wide</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>52.2</td>
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<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>82.6</td>
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<tr>
<td>Piperacillin/tazobactam</td>
<td>97.3</td>
</tr>
<tr>
<td>First-generation cephalosporin</td>
<td>78.5</td>
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<tr>
<td>Cefuroxime</td>
<td>90.3</td>
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<td>Ceftriaxone</td>
<td>97.4</td>
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<td>Ceftazidime</td>
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<td>Cefepime</td>
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<td>Imipenem</td>
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<tr>
<td>Tobramycin</td>
<td>93.4</td>
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<td>Trimethoprim/sulfamethoxazole</td>
<td>70.2</td>
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<td>Ciprofloxacin</td>
<td>83.8</td>
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<tr>
<td>Tetracycline</td>
<td>66.2</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Staphylococcus aureus (n=1,231)</th>
<th>Coagulase-negative staphylococci (n=1,430)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>96.3</td>
<td>92.9</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>24.0</td>
<td>20.5</td>
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<td>Oxacillin</td>
<td>96.3</td>
<td>92.9</td>
</tr>
<tr>
<td>Amikacin</td>
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<td>97.5</td>
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<tr>
<td>Gentamicin</td>
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<td>Tobramycin</td>
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<td>94.5</td>
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<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>98.9</td>
<td>97.0</td>
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<td>Ciprofloxacin</td>
<td>93.1</td>
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<td>Erythromycin</td>
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<td>Clindamycin</td>
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<td>Rifampicin</td>
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<td>97.4</td>
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<tr>
<td>Vancomycin/Teicoplanin</td>
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<td>100</td>
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</table>
### Table 2: Differences in susceptibility rates of community-acquired and nosocomial isolates.

<table>
<thead>
<tr>
<th></th>
<th>Escherichia coli</th>
<th>Pseudomonas aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>community-acquired</td>
<td>nosocomial</td>
</tr>
<tr>
<td><strong>Ampicillin</strong></td>
<td>55.70 [52.05-59.31]</td>
<td>48.47 [45.40-51.55]</td>
</tr>
<tr>
<td><strong>Amoxicillin/clavulanic acid</strong></td>
<td>85.85 [83.12-88.29]</td>
<td>80.60 [78.05-82.97]</td>
</tr>
<tr>
<td><strong>Piperacillin/tazobactam</strong></td>
<td>98.50 [97.33-99.25]</td>
<td>96.50 [95.18-97.54]</td>
</tr>
<tr>
<td>First-generation cephalosporin</td>
<td>82.38 [79.44-85.07]</td>
<td>76.24 [73.52-78.81]</td>
</tr>
<tr>
<td><strong>Cefuroxime</strong></td>
<td>92.94 [89.68-95.42]</td>
<td>89.04 [86.01-91.16]</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong></td>
<td>97.94 [96.63-98.84]</td>
<td>97.16 [95.94-98.09]</td>
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<tr>
<td><strong>Ceftazidime</strong></td>
<td>97.60 [96.24-98.57]</td>
<td>96.58 [95.30-97.59]</td>
</tr>
<tr>
<td><strong>Cefepime</strong></td>
<td>98.83 [97.04-99.68]</td>
<td>96.72 [94.81-98.08]</td>
</tr>
<tr>
<td><strong>Imipenem</strong></td>
<td>100.00 [99.50-100.00]</td>
<td>100.00 [99.64-100.00]</td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td>100.00 [99.49-100.00]</td>
<td>100.00 [99.94-100.00]</td>
</tr>
<tr>
<td><strong>Tobramycin</strong></td>
<td>95.10 [93.27-96.54]</td>
<td>91.80 [89.94-93.40]</td>
</tr>
<tr>
<td><strong>Trimethoprim/sulfamethoxazole</strong></td>
<td>69.65 [66.19-72.95]</td>
<td>67.22 [64.26-70.08]</td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td>94.38 [81.55-86.92]</td>
<td>83.27 [80.84-85.51]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Staphylococcus aureus</th>
<th>Coagulase-negative staphylococci</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>community-acquired</td>
<td>nosocomial</td>
</tr>
<tr>
<td><strong>Amoxicillin/clavulanic acid</strong></td>
<td>95.73 [94.11-97.01]</td>
<td>97.23 [95.88-98.24]</td>
</tr>
<tr>
<td><strong>Oxacillin</strong></td>
<td>95. 64 [94.01-96.93]</td>
<td>97.25 [95.91-98.25]</td>
</tr>
<tr>
<td>Medication</td>
<td>Mean 1 [95% CI]</td>
<td>Mean 2 [95% CI]</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>98.91 [97.94-99.50]</td>
<td>98.45 [97.36-99.17]</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>98.67 [97.62-99.33]</td>
<td>98.93 [97.97-99.50]</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>92.19 [90.10-93.96]</td>
<td>91.96 [89.86-93.74]</td>
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<tr>
<td>Clindamycin</td>
<td>98.36 [97.22-99.13]</td>
<td>98.02 [96.81-98.84]</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>99.75 [99.09-99.97]</td>
<td>99.50 [98.74-99.86]</td>
</tr>
<tr>
<td>Vancomycin/Teicoplanin</td>
<td>100.00 [99.55-100.00]</td>
<td>99.88 [99.34-100.00]</td>
</tr>
</tbody>
</table>
**FIGURE LEGENDS**

**Figure 1**

**Unit-specific benchmark of antibiotic susceptibility.** Prevalence of susceptibility to various antibiotics among *Escherichia coli* recovered from different hospital sites (A-F: intensive care units, 1-8: general wards, ALL: entire hospital). Data presented as percentage of susceptible isolates ± 95% confidence interval (one-sided, 97.5 % confidence interval where susceptibility rate=100%).

**Figure 2**

**Comparison of antibiotic susceptibility in intensive care units and general wards.** Prevalence of susceptibility to various antibiotics among *Escherichia coli* and *Pseudomonas aeruginosa* recovered from intensive care units and general wards. Data presented as percentage of susceptible isolates ± 95% confidence interval (one-sided, 97.5 % confidence interval where susceptibility rate=100%).

**Figure 3**

**Difference of antibiotic susceptibility of subsequent isolates.** Prevalence of susceptibility of first, follow-up (identified >2 and ≤10 days after first isolate) and all isolates (including repeat isolates) to various antibiotics among *Escherichia coli* and *Pseudomonas aeruginosa*. Data presented as percentage of susceptible isolates ± 95% confidence interval (one-sided, 97.5 % confidence interval where susceptibility rate=100%).

**Figure 4**

**Change of antibiotic susceptibility during hospitalization.** Changes in the susceptibility to gentamicin, rifampicin and oxacillin in the course of time after
hospital admission among first isolates of coagulase-negative staphylococci (upper panel) and to piperacillin/tazobactam, amoxicillin/clavulanic acid (middle panel) and ceftriaxone, ciprofloxacin (lower panel) among first isolates of *Escherichia coli*. Data presented as percentage of susceptible isolates ± 95% confidence interval (one-sided, 97.5% confidence interval where susceptibility rate = 100%). *p < 0.05 compared to the susceptibility rate at days 1-3.

**Figure 5**

**Susceptibility of pathogens recovered from different anatomic locations.**

Prevalence of susceptibility to various antibiotics among *Pseudomonas aeruginosa* and *Escherichia coli* recovered from different clinical specimens. Data presented as percentage of susceptible isolates ± 95% confidence interval (one-sided, 97.5% confidence interval where susceptibility rate = 100%).
Figure 1

**Escherichia coli**

- **Amoxicillin/clavulanic acid**
  - Percentage of susceptible isolates
  - Amoxicillin/clavulamic acid, p = 0.003

- **Piperacillin/tazobactam**
  - Percentage of susceptible isolates
  - Piperacillin/tazobactam, \( p = 0.006 \)

- **Ciprofloxacin**
  - Percentage of susceptible isolates
  - Ciprofloxacin, \( p < 0.001 \), \( p = 0.011 \), \( p = 0.018 \)

- **Trimethoprim/sulfamethoxazole**
  - Percentage of susceptible isolates
  - Trimethoprim/sulfamethoxazole, \( p = 0.009 \), \( p = 0.029 \)

- **Meropenem**
  - Percentage of susceptible isolates

- **Ceftriaxone**
  - Percentage of susceptible isolates
Figure 2

**Escherichia coli**

Percentage of susceptible isolates

- Ciprofloxacin
- Piperacillin/tazobactam
- Ceftriaxone
- Ceftazidime
- Imipenem
- Meropenem
- Tobramycin

**Pseudomonas aeruginosa**

Percentage of susceptible isolates

- Ciprofloxacin
- Piperacillin/tazobactam
- Ceftazidime
- Cefepime
- Imipenem
- Meropenem
- Tobramycin

Legend:
- General wards
- ICUs

$p < 0.001$  $p = 0.004$
Figure 3

**Escherichia coli**

- Amoxicillin/Clavulanic acid
- Piperacillin/Tazobactam
- Ceftriaxone
- Imipenem
- Tobramycin
- Ciprofloxacin

**Pseudomonas aeruginosa**

- Piperacillin/Tazobactam
- Cefazidime
- Cefepime
- Meropenem
- Tobramycin
- Ciprofloxacin

- First isolate
- Follow-up isolates days 0-2
- Follow-up isolates days 3-10
- All isolates
Figure 4

**coagulase-negative staphylococci**

- **Rifampicin**
- **Gentamicin**
- **Oxacillin**

<table>
<thead>
<tr>
<th>Day Range</th>
<th>n</th>
<th>Number of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>377</td>
<td></td>
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<tr>
<td>4-6</td>
<td>143</td>
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<td>7-9</td>
<td>161</td>
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<tr>
<td>10-12</td>
<td>137</td>
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<tr>
<td>13-15</td>
<td>102</td>
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</tr>
<tr>
<td>16-18</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>19-21</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

**Percentage of susceptible isolates**

**Escherichia coli**

- **Piperacillin/tazobactam**
- **Amoxicillin/clavulanic acid**

<table>
<thead>
<tr>
<th>Day Range</th>
<th>n</th>
<th>Number of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>701</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>141</td>
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<td>7-9</td>
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<tr>
<td>13-15</td>
<td>68</td>
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</tr>
<tr>
<td>16-18</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>19-21</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

**Percentage of susceptible isolates**

**Escherichia coli**

- **Ciprofloxacin**
- **Ceftriaxone**

<table>
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<tr>
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<td>43</td>
<td></td>
</tr>
<tr>
<td>19-21</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>
Figure 5

Escherichia coli tested against ciprofloxacin

\[ p < 0.001 \]

Pseudomonas aeruginosa tested against ciprofloxacin

\[ p = 0.020 \]

Escherichia coli tested against trimethoprim/sulfamethoxazole

\[ p = 0.001 \]

Pseudomonas aeruginosa tested against ceftazidime (1) and cefepime (2)

\[ p = 0.012 \]

Escherichia coli tested against amoxicillin/clavulanic acid

\[ p < 0.001 \]

Pseudomonas aeruginosa tested against imipenem (1) and meropenem (2)

\[ p = 0.049 \]

Escherichia coli tested against piperacillin/tazobactam

Pseudomonas aeruginosa tested against piperacillin/tazobactam

\[ p = 0.001 \]