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

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***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.**

Keywords: antibacterial resistance, benchmarking, methodology

Introduction

Antibiotic resistance rates vary widely between countries,[1–3] within countries[4] and between as well as within healthcare institutions.[5] The worldwide emergence of antibiotic resistance due to increased and inappropriate antibiotic use reduces the treatment options and the overall efficacy of antimicrobials.[2,6] In patients with presumed acute infection, initial empirical antibiotic therapy, before the results of pathogen identification and susceptibility testing are available, is selected based on individual patient 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 (SRs).[5,7] The choice of empirical antibacterial therapy in hospitalized patients is guided by institution-specific cumulative antibiogram reports, which compile mean

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SRs 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.[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 SRs.[5] Incorrect initial empirical treatment may affect outcome, particularly in critically ill patients.[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 SRs, anatomical 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 bed tertiary care teaching hospital. It covers all medical specialties except paediatrics and orthopaedics. Six intensive care units (ICUs) (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 SRs were assessed and recorded during routine clinical patient care for all diagnostic bacterial isolates obtained from inpatients hospitalized in ICUs and general wards between 1 July 2005 and 30 June 2007 and were analysed retrospectively. For comparisons of nosocomial and community-acquired isolates, isolates from patients spending >24 h in the emergency unit, its observation ward or surgical observation wards were also included. Screening isolates (for example, samples that were analysed 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* (MRSA) and extended-spectrum β-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.[11] Susceptibility testing of bacterial isolates was performed by the disc diffusion method; zone diameters were interpreted according to the CLSI (formerly the NCCLS) guidelines.[11] 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 anatomical site of specimen recovery (blood culture, urinary, respiratory or other) and the year of collection. Unless specified otherwise, SRs of first isolates are reported according to the recently published CLSI guidelines.[8] 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 anatomical site of infection was required to be included in the analysis, as recommended.[8]

Among the repeat isolates, we analysed the first follow-up isolates in two groups, which were defined *a priori*, these groups were 'early' follow-up isolates collected between days 0 and 2 after the first isolate, and 'late' follow-up isolates collected >2 or ≤10 days after the first isolate.

Nosocomial isolates were defined as isolates that were collected more than 48 h after hospital admission and <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 h 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 analysing data on pathogen susceptibility from different anatomical locations.

Antimicrobial SRs of all bacterial isolates were determined, but we limit our report to the analyses of *Escherichia coli*, *Pseudomonas aeruginosa*, *S. 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, TX, USA) 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 <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, 7965 were first, 1201 were follow-up isolates (according to our definition) and 7115 were other repeat isolates.

Unit-specific versus hospital-wide cumulative antibiograms

Table 1 displays the range of hospital-unit-specific SRs, i.e. the mean rates of the unit with the lowest and the unit with the highest SR, in comparison with the mean hospital-wide cumulative SR of first isolates of *E. coli*, *P. aeruginosa*, *S. aureus* and coagulase-negative staphylococci. Figure 1 depicts the mean SRs of *E. coli* in each single ICU and ward.

We detected significant differences in the overall SRs 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,

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Table 1. Hospital-wide antibiograms and range of unit-specific SRs of the departments with the lowest and the highest rates

	Mean susceptibility rates (% of isolates)					
	E. coli ($n = 1326$)			*P. aeruginosa* ($n = 567$)		
	hospital-wide	lowest	highest	hospital-wide	lowest	highest
Ampicillin	52.2	40.0	69.4	0.0	0	0
Amoxicillin/clavulanic acid	82.6	62.5	92.7	0.5	0.0	3.3
Piperacillin/tazobactam	97.3	87.5	100	94.6	85.0	100
First-generation cephalosporin	78.5	71.7	96.8	0.2	0.0	1.4
Cefuroxime	90.3	83.7	95.8	1.0	0.0	4.1
Ceftriaxone	97.4	94.1	100	11.8	0.0	22.7
Ceftazidime	97.0	92.5	100	93.4	89.7	100
Cefepime	97.5	97.0	100	92.9	87.2	96.2
Imipenem	100.0	100	100	78.6	54.2	100
Meropenem	100.0	100	100	92.5	80.4	100
Tobramycin	93.4	85.7	98.4	95.8	92.6	100
Trimethoprim/sulfamethoxazole	70.2	58.1	86.1	3.7	0.0	11.1
Ciprofloxacin	83.8	64.5	95.1	88.5	80.0	95.2
Tetracycline	66.2	61.6	82.1	5.5	0.0	16.7
	S. aureus ($n = 1231$)			coagulase-negative staphylococci ($n = 1430$)		
Amoxicillin/clavulanic acid	96.3	92.9	100			
Ampicillin	24.0	20.5	31.0	15.7	0.0	24.0
Oxacillin	96.3	92.9	100	41.0	12.8	60.0
Amikacin	99.3	97.5	100	86.9	53.1	98.6
Gentamicin	98.4	96.2	100	67.3	12.8	73.1
Tobramycin	96.7	94.5	100	56.5	8.3	77.1
Trimethoprim/sulfamethoxazole	98.9	97.0	100	58.0	10.6	76.0
Ciprofloxacin	93.1	87.5	100	48.4	8.7	93.1
Erythromycin	92.3	88.6	95.1	41.3	17.0	57.6
Clindamycin	98.2	95.8	100	65.7	53.1	96.6
Rifampicin	99.6	97.4	100	84.5	72.9	96.9
Vancomycin/teicoplanin	100	100	100	99.3	97.3	100

significant differences across departments were only detected for penicillin resistance rates.

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

- mean *E. coli* SR to amoxicillin/clavulanic acid, ranging from 62.5% (thoracic and transplant surgery ICU) to 92.7% (department of neurosurgery);
- mean *E. coli* SR to ciprofloxacin, ranging from 64.5% (department of dermatology) to 95.1% (department of neurosurgery);
- mean *E. coli* SR to trimethoprim/sulfamethoxazole, ranging from 58.1% (department of rheumatology) to 86.1% (department of neurology);
- mean *P. aeruginosa* SR to piperacillin/tazobactam, ranging from 85.0% (medical ICU) to 100% (departments of dermatology and gynaecology and obstetrics);
- mean *P. aeruginosa* SR to imipenem and meropenem, ranging from 54.2% (thoracic and transplant surgery ICU) to 100% (department of gynaecology and obstetrics) and from 80.4 (thoracic and transplant surgery ICU) to 100% (department of gynaecology and obstetrics), respectively;
- mean *P. aeruginosa* SR to ciprofloxacin, ranging from 80.0 (medical ICU) to 95.2% (trauma ICU).

ICUs versus general wards

Figure 2 contrasts the SRs of first isolates of *E. coli* and *P. aeruginosa* recovered from ICUs (*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

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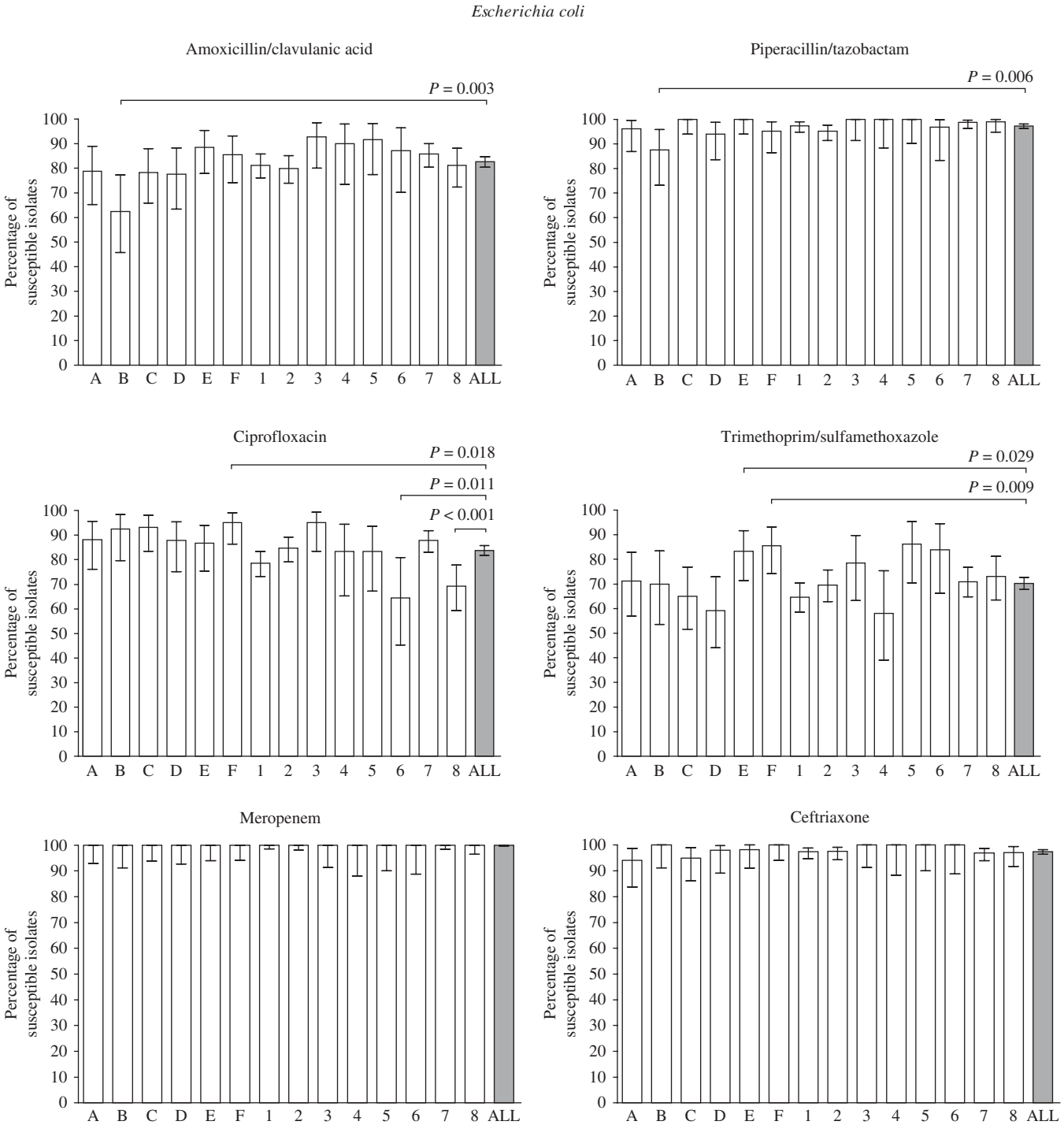

Figure 1. Unit-specific benchmark of antibiotic susceptibility. Prevalence of susceptibility to various antibiotics among *E. coli* recovered from different hospital sites (A–F: ICUs, 1–8: general wards, ALL: entire hospital). Data are presented as percentage of susceptible isolates ± 95% confidence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

the first isolate, respectively, versus all isolates of *E. coli* and *P. aeruginosa*.

First isolates of *E. coli* ($n = 1326$) and *P. aeruginosa* ($n = 567$) were significantly more susceptible to various antibiotics than follow-up isolates [*E. coli*, $n = 221$ ('early' follow-up isolates) and $n = 180$ ('late' follow-up isolates), respectively, *P. aeruginosa*, $n = 163$ ('early' follow-up isolates) and $n = 165$ ('late' follow-up isolates), respectively, or all isolates (*E. coli*, $n = 2491$; *P. aeruginosa*, $n = 1768$)]. Except for the SR of *E. coli* tested against ampicillin [SR 30.98% ('late' follow-up isolates) and 40.97% (all isolates), respectively, $P = 0.013$], no significant differences in SRs were detected between 'late' follow-up and all isolates.

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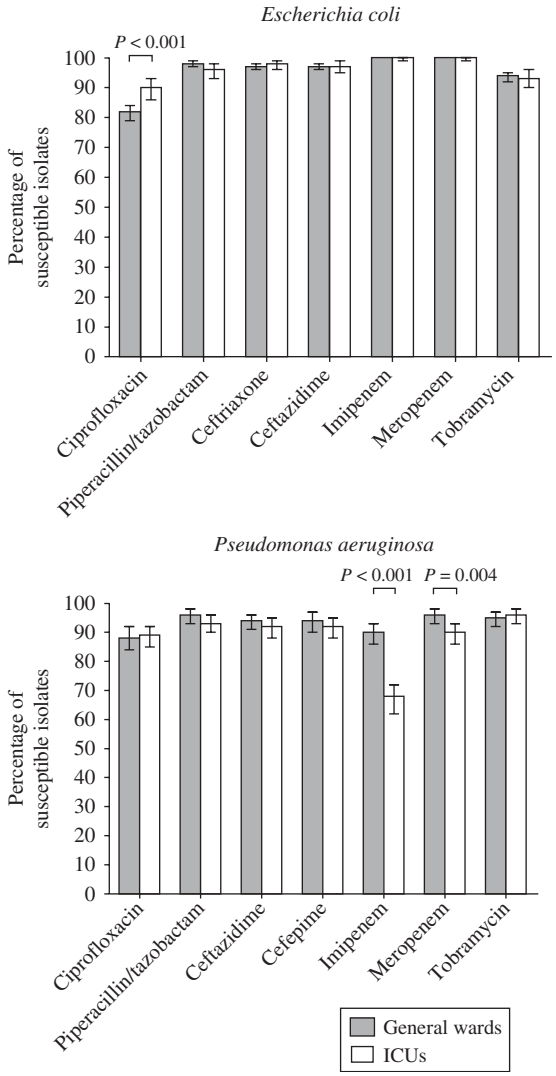

Figure 2. Comparison of antibiotic susceptibility in ICUs and general wards. Prevalence of susceptibility to various antibiotics among *E. coli* and *P. aeruginosa* recovered from ICUs and general wards. Data are presented as percentage of susceptible isolates ± 95% confidence interval (one-sided, 97.5% confidence interval where SR= 100%).

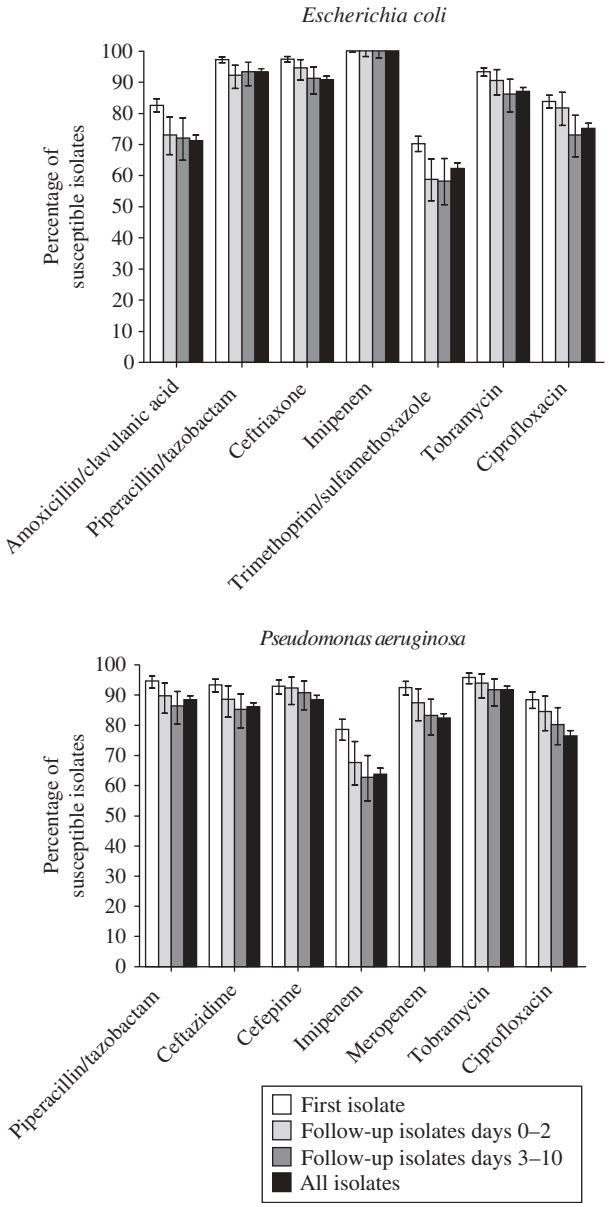

Figure 3. Difference in antibiotic susceptibility of subsequent isolates. Prevalence of susceptibility of first, follow-up (identified >2 and ≤10 days after first isolate) and all isolates (including repeat isolates) to various antibiotics among *E. coli* and *P. aeruginosa*. Data are presented as percentage of susceptible isolates ± 95% confidence interval (one-sided, 97.5% confidence interval where SR=100%).

Community-acquired versus nosocomial isolates

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

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 SRs during the course of hospitalization could be observed in coagulase-negative staphylococci tested against gentamicin, oxacillin and rifampicin, but not in *E. coli* tested against ciprofloxacin, ceftriaxone, amoxicillin/clavulanic acid or piperacillin/tazobactam. Data on changes of SRs of *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 SRs of organisms recovered from different anatomical sites (Figure 5). For example,

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Table 2. Differences in SRs of community-acquired and nosocomial isolates

	Mean susceptibility rates (% of isolates) (95% confidence interval)					
	E. coli			*P. aeruginosa*		
	community-acquired ($n = 729$)	nosocomial ($n = 1017$)	*P* value	community-acquired ($n = 219$)	nosocomial ($n = 485$)	*P* value
Ampicillin	55.70 (52.05–59.31)	48.47 (45.40–51.55)	0.003	0.45 (0.01–2.51)	0.21 (0.00–1.14)	0.527
Amoxicillin/clavulanic acid	85.85 (83.12–88.29)	80.60 (78.05–82.97)	0.004	1.36 (0.28–3.93)	0.61 (0.13–1.79)	0.381
Piperacillin/tazobactam	98.50 (97.33–99.25)	96.50 (95.18–97.54)	0.010	96.36 (92.96–98.42)	94.18 (91.74–96.07)	0.273
First-generation cephalosporin	82.38 (79.44–85.07)	76.24 (73.52–78.81)	0.002	0.00 (0.00–1.67)	0.41 (0.05–1.47)	1.000
Cefuroxime	92.94 (89.68–95.42)	89.04 (86.01–91.16)	0.071	1.66 (0.34–4.77)	1.63 (0.39–1.97)	1.000
Ceftriaxone	97.94 (96.63–98.84)	97.16 (95.94–98.09)	0.354	10.76 (7.02–15.59)	12.05 (9.32–15.24)	0.707
Ceftazidime	97.60 (96.24–98.57)	96.58 (95.30–97.59)	0.262	94.12 (90.15–96.83)	93.00 (90.40–95.08)	0.631
Cefepime	98.83 (97.04–99.68)	96.72 (94.81–98.08)	0.069	94.05 (89.61–96.99)	93.24 (90.49–95.40)	0.860
Imipenem	100.00 (99.50–100.00)	100.00 (99.64–100.00)		87.95 (82.95–91.90)	76.65 (72.69–80.28)	<0.001
Meropenem	100.00 (99.49–100.00)	100.00 (99.94–100.00)		94.09 (90.11–96.82)	92.17 (89.45–94.37)	0.436
Tobramycin	95.10 (93.27–96.54)	91.80 (89.94–93.40)	0.007	94.14 (90.19–96.85)	95.93 (93.78–97.49)	0.336
Trimethoprim/sulfamethoxazole	69.65 (66.19–72.95)	67.22 (64.26–70.08)	0.006	6.36 (3.52–10.45)	3.87 (2.35–5.98)	0.176
Ciprofloxacin	94.38 (81.55–86.92)	83.27 (80.84–85.51)	0.566	87.00 (81.86–91.11)	88.17 (85.03–90.85)	0.713
	S. aureus			coagulase-negative staphylococci		
	community-acquired ($n = 826$)	nosocomial ($n = 836$)	*P* value	community-acquired ($n = 372$)	nosocomial ($n = 1261$)	*P* value
Amoxicillin/clavulanic acid	95.73 (94.11–97.01)	97.23 (95.88–98.24)	0.109			
Ampicillin	26.08 (23.13–29.21)	23.16 (20.35–26.16)	0.173	30.99 (26.40–35.88)	13.21 (11.42–15.17)	<0.001
Oxacillin	95.64 (94.01–96.93)	97.25 (95.91–98.25)	0.085	73.47 (68.71–77.86)	35.70 (33.09–38.38)	<0.001
Gentamicin	98.91 (97.94–99.50)	98.45 (97.36–99.17)	0.521	87.53 (83.77–90.69)	63.22 (60.56–65.82)	<0.001
Trimethoprim/sulfamethoxazole	98.67 (97.62–99.33)	98.93 (97.97–99.50)	0.659	75.33 (70.66–79.60)	57.88 (55.26–60.46)	<0.001
Erythromycin	92.19 (90.10–93.96)	91.96 (89.86–93.74)	0.926	60.06 (54.62–65.32)	39.24 (36.47–42.06)	<0.001
Clindamycin	98.36 (97.22–99.13)	98.02 (96.81–98.84)	0.709	83.28 (78.85–87.12)	63.16 (60.38–65.88)	<0.001
Rifampicin	99.75 (99.09–99.97)	99.50 (98.74–99.86)	0.687	96.15 (93.51–97.94)	82.86 (80.61–84.95)	<0.001
Vancomycin/teicoplanin	100.00 (99.55–100.00)	99.88 (99.34–100.00)	1.000	99.47 (98.09–99.94)	99.22 (98.57–99.63)	1.000

respiratory isolates of *E. coli* ($n = 114$) were significantly more often susceptible to ciprofloxacin than first *E. coli* isolates overall ($n = 1768$; SR 92.11% and 83.83%, respectively, $P < 0.001$). The SR to trimethoprim/sulfamethoxazole of *E. coli* isolates recovered from blood cultures ($n = 94$) was significantly lower than the respective overall SR (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 SR 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 SRs of important bacterial pathogens across various hospital departments and between ICUs and general wards. Furthermore, follow-up isolates (identified between more than 48 h and 10 days

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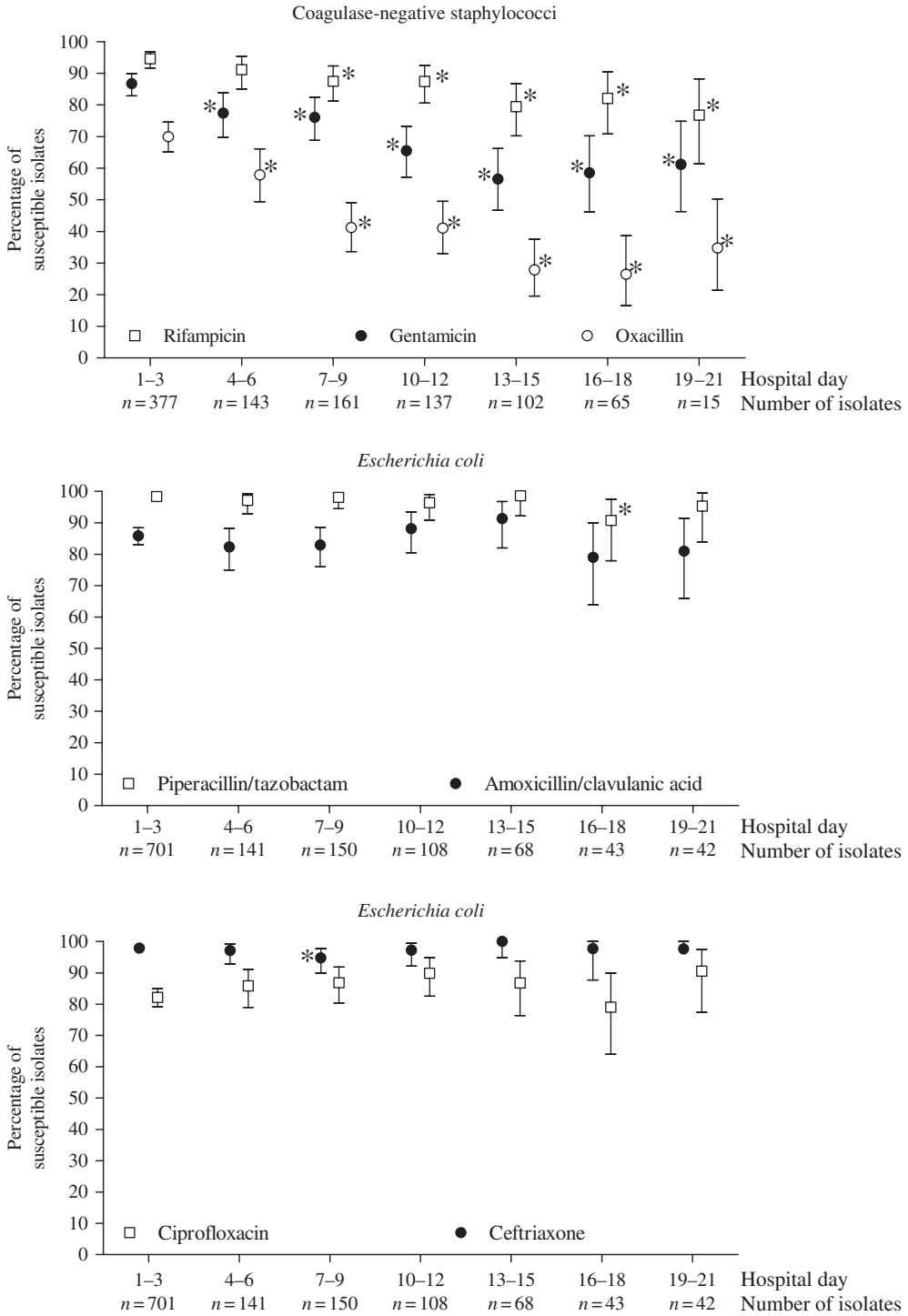

Figure 4. Change of antibiotic susceptibility during hospitalization. Changes in the susceptibility to gentamicin, rifampicin and oxacillin in the course of time after hospital admission among first isolates of coagulase-negative staphylococci (upper panel) and to piperacillin/tazobactam, amoxicillin/clavulanic acid (middle panel) and ceftriaxone, ciprofloxacin (lower panel) among the first isolates of *E. coli*. Data are presented as percentage of susceptible isolates $\pm$95% confidence interval (one-sided, 97.5% confidence interval where SR = 100%). *$P < 0.05$ compared with the SR at days 1–3.

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 SRs of some bacterial species. Finally, isolates from different anatomical sites differed in their SRs.

SRs of bacterial isolates from certain departments may differ from those of a hospital overall, as previously shown,[5] but comprehensive unit-specific data are scarce in the literature. We found striking differences of cumulative antibiograms across different departments of our hospital. For example, mean SRs of

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E. coli to ciprofloxacin ranged between 64.5% and 95.1%, and those of *P. 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 the findings of previous studies reporting differences in the prevalence of antimicrobial resistance among various pathogens between ICUs, non-ICU units, overall hospital data and between different ICUs of a single institution.[5,12–14]

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.[15–17] Also, specimen-collection practices, i.e. the frequency of repeat cultures during patients' evaluation or the use of surveillance cultures in ICUs, may influence the SRs. Therefore, guidelines to prepare cumulative antibiogram reports recommend exclusion of repeat isolates per episode and emphasize that the 'first isolate per patient approach' has 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 the management of prolonged or re-occurring 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 analysing microbiological laboratory data sets.[8] 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

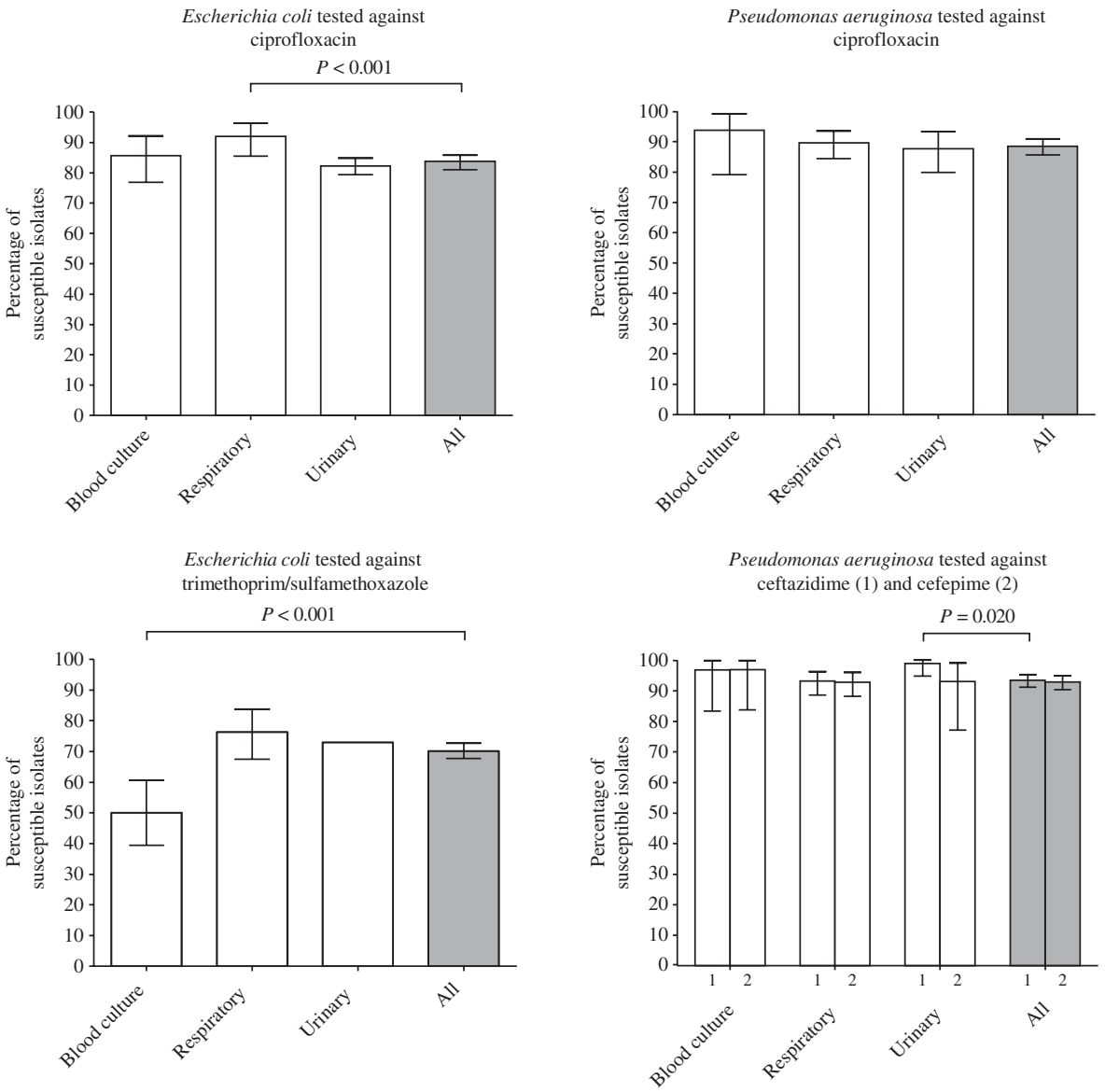

Figure 5. Susceptibility of pathogens recovered from different anatomical locations. Prevalence of susceptibility to various antibiotics among *P. aeruginosa* and *E. coli* recovered from different clinical specimens. Data are presented as percentage of susceptible isolates ± 95% confidence interval (one-sided, 97.5% confidence interval where SR = 100%).

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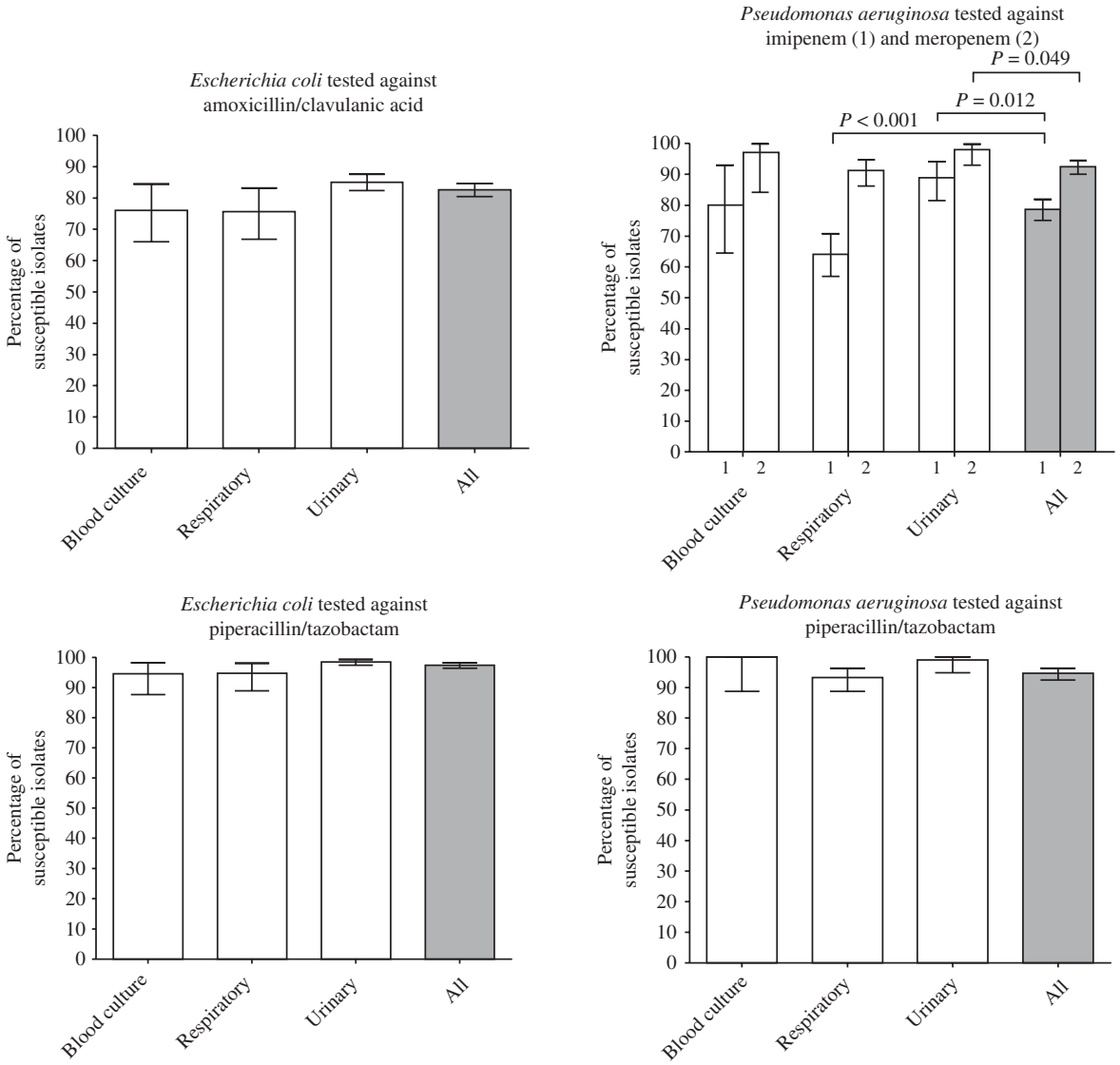

Figure 5. Continued.

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 h and 10 days after the first one) which is expected to exclude most duplicate isolates. We found that, in general, mean SRs of 'late' follow-up isolates were lower than the 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 important information in addition to the first isolate antibiograms.

Isolates from nosocomial infections are generally regarded as less susceptible to antibiotics than community-acquired organisms, but this is not true for all bacteria or for all hospital sites and geographic areas.[18–20] 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.[21,22] We observed that the mean SRs 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 MRSA at our institution and in the surrounding region is ~3%, which is 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

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of empirical antibacterial therapy may not by itself be a sufficient criterion for the use of broad-spectrum antibiotics or MRSA-covering substances.

Whether the anatomical 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.[5,23,24] We found variations in SRs 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.[5] Because laboratory datasets 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 SRs, specifically within an institution, during different phases of hospitalization, or of infections at different anatomical 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 home institution may be supported by depicting institution-specific data for selected examples of frequent bacterial isolates with decreasing SRs during the course of hospitalization.

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