

Revised Abstract

Background: The Study for Monitoring Antimicrobial Resistance Trends (SMART) has monitored activity of amikacin (AK), ampicillin-sulbactam (AS), cefepime (CPE), cefotaxime (CFT), ceftazidime (CAZ), ceftriaxone (CAX), ciprofloxacin (CP), ertapenem (ETP), imipenem (IMP), levofloxacin (LVX), and piperacillin-tazobactam (PT) vs. aerobic gram-negative bacteria (GNB) from intra-abdominal infections (IAIs) for many years. This report summarizes susceptibility levels and epidemiology for key IAI pathogens cultured from general pediatric medical wards and pediatric ICUs globally. **Methods:** 1,248 GNB were collected from pediatric IAIs by 113 labs in 40 countries from 2008 to 2010. MICs were determined by broth microdilution and interpreted using CLSI guidelines. Susceptibility rates (%S) for isolates were determined for species with ≥10 isolates. **Results:** 62% of isolates came from general pediatric wards and 38% from pediatric ICUs. Overall ESBL+ rate was 11.0% for *E. coli*, and 38.9% for *K. pneumoniae*. The susceptibilities of the top 10 species are listed in the table below with %S ≥90 highlighted.

Rank	Organism	n	AK	AS	CPE	CFT	CFX	CAZ	CAX	CP	ETP	IMP	LVX	PT
1	<i>E. coli</i> , ESBL-	617	100	49	100	96	95	96	96	92	99	99	92	95
1	<i>E. coli</i> , ESBL+	76	84	8	11	0	82	22	0	30	91	97	32	78
2	<i>K. pneumoniae</i> , ESBL-	80	96	71	98	93	90	94	94	94	95	98	96	91
2	<i>K. pneumoniae</i> , ESBL+	51	69	2	27	6	78	8	6	55	84	94	76	45
3	<i>P. aeruginosa</i>	123	90	na	85	na	na	80	na	85	na	85	86	89
4	<i>E. cloacae</i>	87	97	17	86	51	8	55	51	93	69	98	97	67
5	<i>K. oxytoca</i> , ESBL-	42	100	67	100	98	95	100	90	98	100	100	100	90
5	<i>K. oxytoca</i> , ESBL+	1	1/1	0/1	1/1	0/1	1/1	0/1	0/1	1/1	1/1	1/1	1/1	1/1
6	<i>P. mirabilis</i>	24	100	83	100	100	100	100	100	92	100	29	92	100
7	<i>A. baumannii</i>	23	39	43	26	39	na	43	30	35	na	57	48	39
8	<i>E. aerogenes</i>	22	100	14	82	27	14	32	32	82	77	95	95	55
8	<i>C. freundii</i>	22	86	45	86	59	14	64	64	77	95	100	86	77
9	<i>S. marcescens</i>	17	100	24	94	82	59	88	88	94	100	94	100	88

* %S not calculated for n<10; n inhibited/total n are shown; na=not applicable.

Conclusions: Amikacin, imipenem, and ertapenem were the most active drugs *in vitro* against GNB from pediatric IAIs, followed closely by the fluoroquinolones and cefepime. Other 3rd and 4th generation cephalosporins were often <90% active. ESBL rates were 38.9% for *K. pneumoniae* and 11.0% for *E. coli*. Therapy for pediatric IAIs should take into consideration local ESBL+ rates since only imipenem and ertapenem inhibited most of these pathogens.

Introduction

Safety concerns pose a challenge for the treatment of pediatric complicated intra-abdominal infections (IAIs). Tetracyclines, such as tigecycline, are contraindicated for infections in children aged <8 years and parenteral fluoroquinolones are not routinely recommended. An ongoing trend away from the traditional aminoglycoside-based triple-antibiotic therapy is driven largely by the fewer infusions required by other regimens. Current recommendations for pediatric patients with complicated IAIs include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftazidime, or cefepime) with metronidazole [1].

The Study for Monitoring Antimicrobial Resistance Trends (SMART) has been monitoring intra-abdominal infections (IAI) for epidemiologic and antimicrobial susceptibility trends globally since 2002. This analysis of SMART data from 2008-2010 describes the occurrence of aerobic gram-negative bacilli (GNB), including extended-spectrum β-lactamase (ESBL) producers, in pediatric IAIs from both general non-ICU wards and ICUs, as well as the susceptibility of these pathogens to ertapenem and comparators.

Materials & Methods

- Participating sites each collected up to 100 consecutive non-selected aerobic gram-negative pathogens from intra-abdominal infections each year of the study. Only one isolate per species per patient was accepted into the study. For this report, 1,248 isolates were collected between 2008 and 2010 at 113 hospitals in 40 countries. 62% of isolates came from general (non-ICU) pediatric wards and 38% from pediatric ICUs.
- Isolates were identified to the species level and sent to a central laboratory (Laboratory International for Microbiology Studies [LIMS], a subsidiary of International Health Management Associates, Inc., Schaumburg, IL, USA) for susceptibility testing and confirmation of identification. Isolates from China collected in 2009-2010 were sent to a central lab in Beijing (Peking Union Medical Center) for susceptibility testing and confirmation of identification, using the same susceptibility testing panels as LIMS.
- Organism collection, transport, confirmation of organism identification, susceptibility testing, and development and management of a centralized database were coordinated by LIMS.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method using MicroScan panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA) [2]. All antimicrobics were supplied by the panel manufacturer.
- MIC interpretive criteria followed published guidelines of the CLSI [3].
- Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, and *Proteus mirabilis* isolates were classified as ESBL producers if there was at least an eight-fold reduction of MIC for ceftazidime or cefotaxime tested in combination with clavulanic acid versus their MICs when tested alone [3].
- Quality controls (QC) were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [3].
- Confidence intervals were calculated using the adjusted Wald method.
- Differences in ESBL-rates percent susceptible between patient locations and regions were evaluated for significance using Fisher's Exact Test, two tailed.
- The Cochran-Armitage test was used to assess linear trends in ESBL rates over time.

References

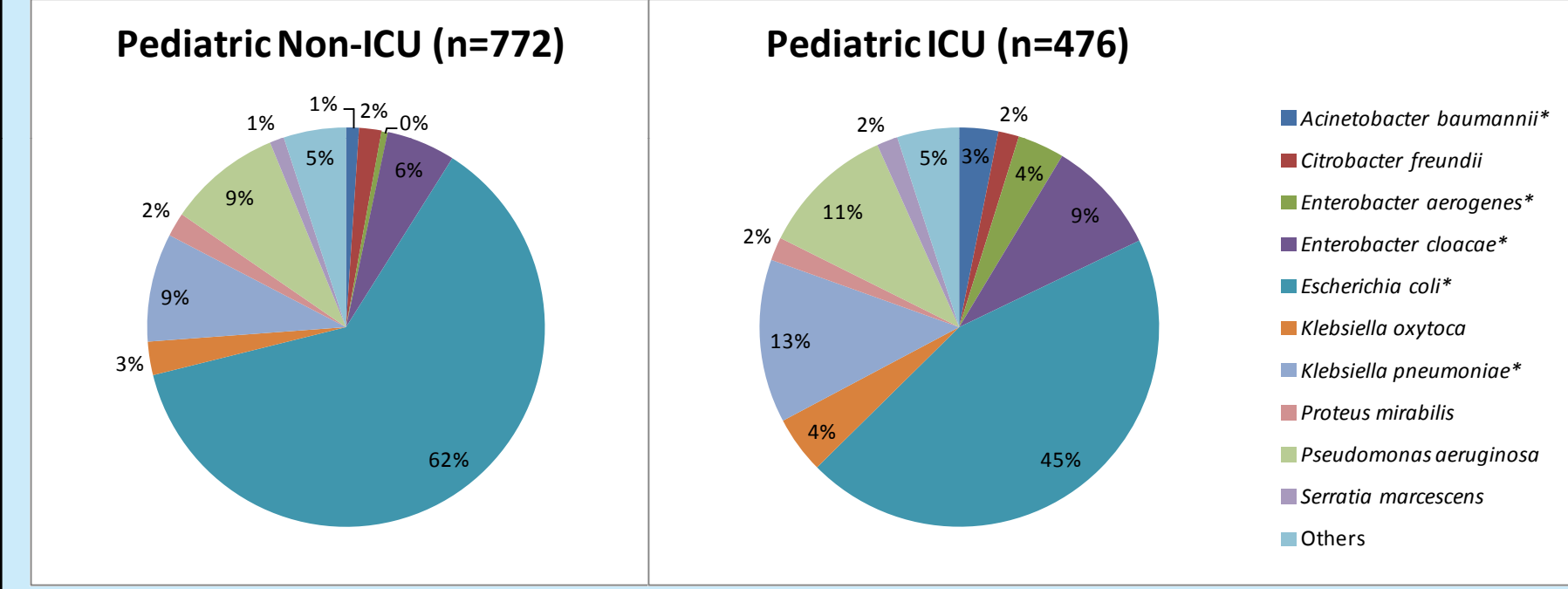
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Acknowledgements

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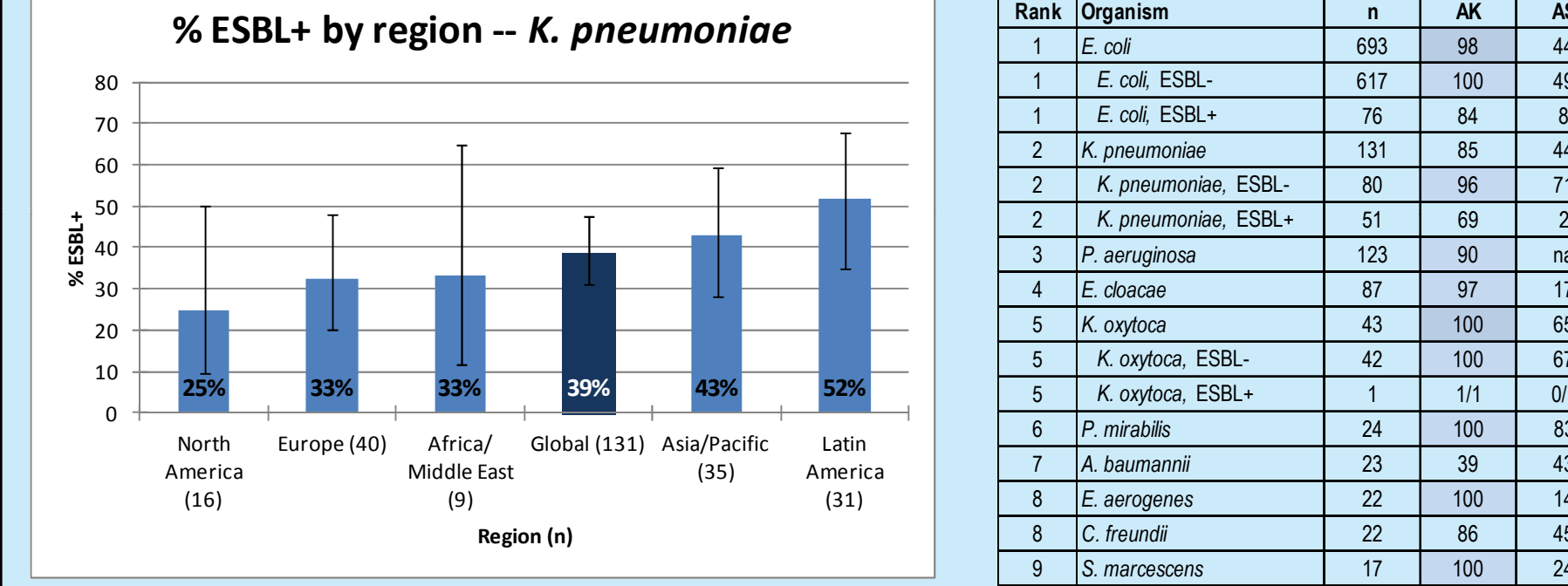
Results

Figure 1. Frequency distribution of species found in pediatric IAIs, by patient location.



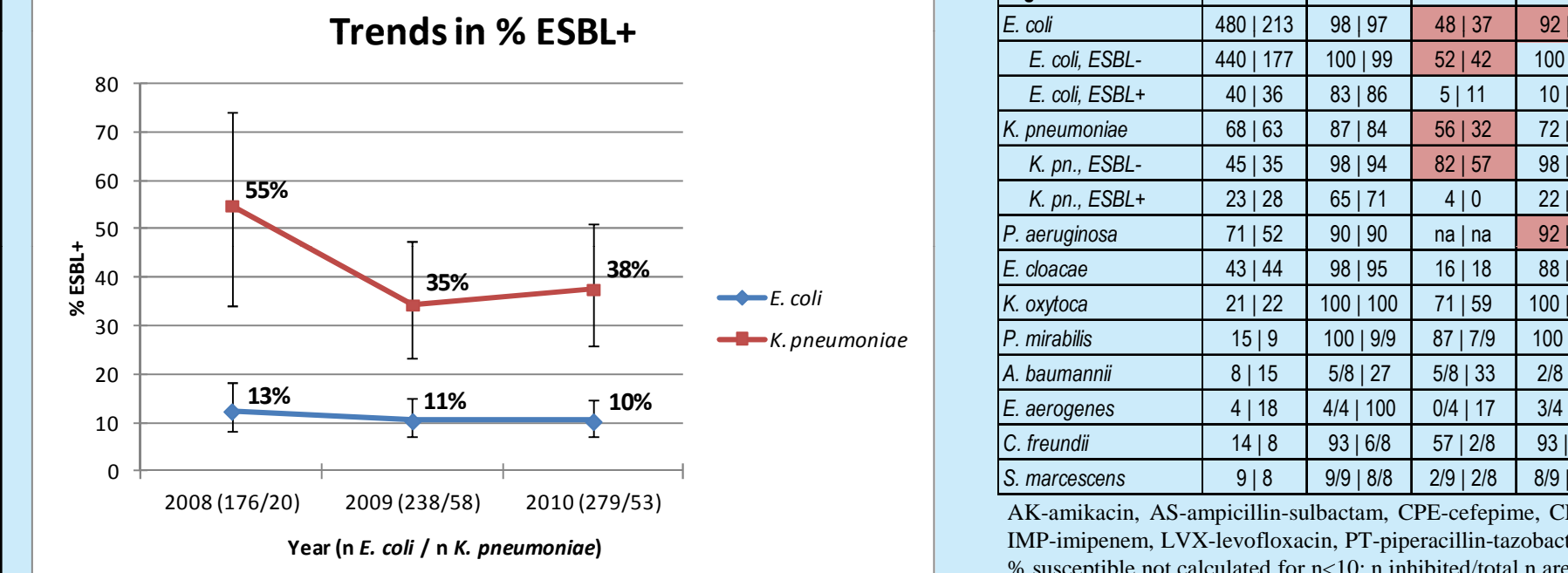
* Significant difference in proportion of species between non-ICU and ICU isolates (p<0.05).

Figure 4. Percentage of ESBL-positive *K. pneumoniae* (pediatric non-ICU wards and ICUs combined) with 95% Confidence Intervals (High and Low), by global region.



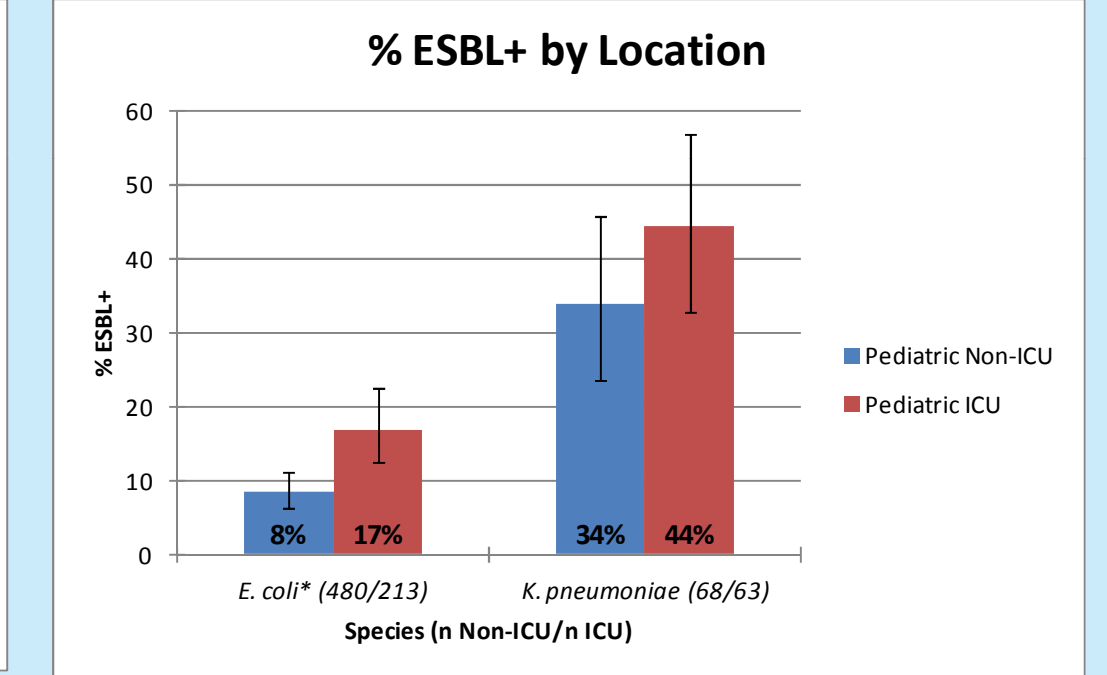
Note: No significant differences in % ESBL+ between regions (p>0.05).

Figure 5. Percentage of ESBL-positive *E. coli* and *K. pneumoniae* (pediatric non-ICU wards and ICUs combined) with 95% Confidence Intervals (High and Low), by year.



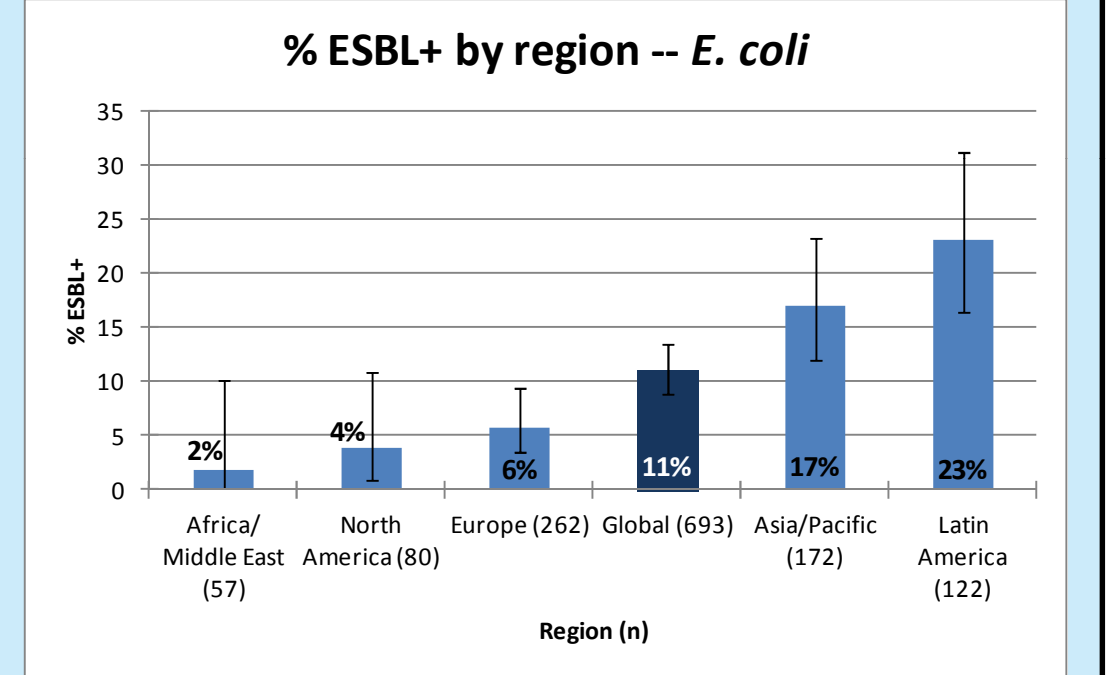
Note: No significant trend found (p>0.05).

Figure 2. Percentage of ESBL-positive *E. coli* and *K. pneumoniae* with 95% Confidence Intervals (High and Low), categorized by pediatric non-ICU vs. ICU location.



* Significant difference in % ESBL+ between non-ICU and ICU isolates (p<0.05).

Figure 3. Percentage of ESBL-positive *E. coli* (pediatric non-ICU wards and ICUs combined) with 95% Confidence Intervals (High and Low), by global region.



Note: All regions with lower ESBL+ rates than the global average were significantly different from those with higher than average rates (p<0.05).

Conclusions

- The top 10 species isolated in pediatric IAIs were the same in non-ICU wards and ICUs, but with statistically significant differences in the relative proportions, with *E. coli* 6 times more prevalent (62%) in non-ICU ward than any other single species and over 3 times (45%) more prevalent in ICU wards.
- The ESBL+ rate in *E. coli*, overall at 11.0%, was significantly lower in pediatric non-ICU wards than in ICUs and also differed significantly between the regions with lower than average ESBL+ rates and those with higher than average rates. Conversely, for ESBL+ *K. pneumoniae* (overall at 38.9%), the differences between locations and regions were not statistically significant (at least in part due to the smaller sample size).
- The apparent downward trend in ESBL rates between 2008 and 2010 was not statistically significant (p<0.05) but should continue to be monitored.
- Amikacin, imipenem, and ertapenem were the most active drugs *in vitro* against gram-negative bacilli from pediatric IAIs, including ESBL-producing isolates. 3rd and 4th generation cephalosporins, fluoroquinolones, and piperacillin-tazobactam continue to be effective against the majority of non-ESBL producing strains, especially in non-ICU patients.
- Therapy for pediatric IAIs should take into consideration local ESBL+ rates, since only imipenem and ertapenem inhibited most of these pathogens.

Table 1. Percent susceptible for the top 10 species isolated in pediatric non-ICU and ICU wards combined.

Rank	Organism	n	AK	AS	CPE	CFT	CFX	CAZ	CAX	CP	ETP	IMP	LVX	PT
1	<i>E. coli</i>	693	98	44	90	85	93	88	86	85	98	99	86	93
1	<i>E. coli</i> , ESBL-	617	100	49	100	96	95	96	96	92	99	99	92	95
1	<i>E. coli</i> , ESBL+	76	84	8	11	0	82	22	0	30	91	97	32	78
2	<i>K. pneumoniae</i>	131	85	44	70	58	85	60	59	78	90	95	88	73
2	<i>K. pneumoniae</i> , ESBL-	80	96	71	98	93	90	94	94	94	95	98	96	91
2	<i>K. pneumoniae</i> , ESBL+	51	69	2	27	6	78	8	6	55	84	94	76	45
3	<i>P. aeruginosa</i>	123	90	na	85	na	na	80	na	85	na	85	86	89
4	<i>E. cloacae</i>	87	97	17	86	51	8	55	51	93	69	98	97	67
5	<i>K. oxytoca</i>	43	100	65	100	95	95	98	88	98	100	100	100	91
5	<i>K. oxytoca</i> , ESBL-	42	100	67	100	98	95	100	90	98	100	100	100	90
5	<i>K. oxytoca</i> , ESBL+	1	1/1	0/1	1/1	0/1	1/1	0/1	0/1	1/1	1/1	1/1	1/1	1/1
6	<i>P. mirabilis</i>	24	100	83	100	100	100	100	100	92	100	29	92	100
7	<i>A. baumannii</i>	23	39	43	26	39	na	43	30	35	na	57	48	39
8	<i>E. aerogenes</i>	22	100	14	82	27	14	32	32	82	77	95	95	55
8	<i>C. freundii</i>	22	86	45	86	59	14	64	64	77	95	100	86	77
9	<i>S. marcescens</i>	17	100	24	94	82	59	88	88	94	100	94	100	88

AK-amikacin, AS-ampicillin-sulbactam, CPE-cefepime, CFT-cefotaxime, CFX-cefoxitin, CAZ-ceftazidime, CAX-ceftaxone, CP-ciprofloxacin, ETP-ertapenem, IMP-imipenem, LVX-levofloxacin, PT-piperacillin-tazobactam, na-not applicable (breakpoint not defined).
% susceptible not calculated for n<10; n inhibited/total n are shown instead.
Values ≥90% are shaded blue.

Table 2. Percent susceptible for the top 10 species isolated in non-ICU wards compared to ICUs.

Organism	n	Pediatric Non-ICU Pediatric ICU												
		AK	AS	CPE	CFT	CFX	CAZ	CAX	CP	ETP	IMP	LVX	PT	
<i>E. coli</i>	480 213	98 97	48 37	92 84	88 79	94 92	92 80	88 80	87 81	99 98	99 99	87 82	95 88	
<i>E. coli</i> , ESBL-	440 177	100 99	52 42	100 99	96 95	95 94	97 95	96 96	92 92	100 99	100 98	92 93	97 90	
<i>E. coli</i> , ESBL+	40 36	83 86	5 11	10 11	0 0	78 86	38 6	0 0	33 28	88 94	95 100	35 28	80 75	
<i>K. pneumoniae</i>	68 63	87 84	56 32	72 68	65 52	81 90	65 56	66 52	78 79	88 94	94 98	90 87	75 71	
<i>K. pn.</i> , ESBL-	45 35	98 94	82 57	98 97	93 91	91 89	96 91	96 91	96 91	98 94	98 97	98 94	93 89	
<i>K. pn.</i> , ESBL+	23 28	65 71	4 0	22 32	9 4	61 93	4 11	9 4	43 64	74 93	87 100	74 79	39 50	
<i>P. aeruginosa</i>	71 52	90 90	na na	92 75	na na	na na	85 73	na na	89 81	na na	92 77	89 83	93 83	
<i>E. cloacae</i>	43 44	98 95	16 18	88 84	56 45	7 9	60 50	56 45	93 93	74 64	95 100	98 95	70 64	
<i>K. oxytoca</i>	21 22	100 100	71 59	100 100	90 100	100 91	95 100	81 95	95 100	100 100	100 100	100 100	86 95	
<i>P. mirabilis</i>	15 9	100 99	87 79	100 99	100 99	100 99	100 99	100 99	87 99	100 99	20 49	87 99	100 99	
<i>A. baumannii</i>	8 15	5/8 2/7	5/8 3/3	2/8 2/7	4/8 3/3	na na	5/8 3/3	2/8 3/3	4/8 2/7	na na	5/8 5/3	5/8 4/0	4/8 3/3	
<i>E. aerogenes</i>	4 18	4/4 10/0	0/4 1/7	3/4 8/3	1/4 2/8	0/4 1/7	1/4 3/3	1/4 3/3	3/4 8/3	4/4 7/2	4/4 9/4	4/4 9/4	2/4 5/6	
<i>C. freundii</i>	14 8	93 6/8	57 2/8	93 6/8	57 5/8	14 1/3	64 5/8	64 5/8	86 5/8	93 8/8				