

# Susceptibility of pediatric isolates of *Escherichia coli* and *Klebsiella pneumoniae*: A global perspective 2004-2010



OB016

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## Revised Abstract

**Background:** *E. coli* (EC) and *K. pneumoniae* (KP) remain important pathogens in pediatric infections while dramatic increases in resistance over the past 10 years in EC and KP, primarily due to the emergence of extended spectrum beta-lactamases (ESBLs), have challenged treatment regimens for many infections caused by EC and KP. The Tigecycline Evaluation and Surveillance Trial (TEST) has been monitoring the susceptibility of pathogens worldwide since 2004. This report summarizes global data from TEST in 2004-2010 for EC and KP isolated from a variety of infection sites in pediatric patients. **Methods:** 1739 cumulative hospital sites in 60 countries collected consecutive isolates of EC and KP from infection sites including blood, urine, wound, intra-abdominal, respiratory and gastrointestinal in 2004-2010. Isolate identification and susceptibility testing was performed at a central laboratory and interpreted using CLSI M100-S21 guidelines, where available, and FDA guidelines for tigecycline. **Results:** 5026 isolates were collected, of which 55% were *E. coli*, and 45% *K. pneumoniae*. Eleven percent of *E. coli* and 23% of *K. pneumoniae* were ESBL+ and exhibited reduced susceptibility profiles. Susceptibility of organisms is shown in the table below. **Bold** numbers highlight % susceptible values  $\geq 90\%$ .

Organism	N	Ak	Cpe	Cax	Lvx	Mer	PT	Tig
<i>E. coli</i> , all	2752	<b>97</b>	<b>91</b>	83	81	<b>99</b>	<b>92</b>	<b>99</b>
<i>E. coli</i> ESBL+	291	85	40	2	40	<b>97</b>	76	<b>99</b>
<i>E. coli</i> ESBL-	2461	<b>99</b>	<b>97</b>	<b>92</b>	85	<b>99</b>	<b>94</b>	<b>99</b>
<i>K. pneumoniae</i> , all	2274	<b>92</b>	82	67	88	<b>96</b>	80	<b>97</b>
<i>K. pneumo.</i> ESBL+	519	76	42	1	73	<b>91</b>	52	<b>95</b>
<i>K. pneumo.</i> ESBL-	1755	<b>96</b>	<b>94</b>	86	<b>92</b>	<b>98</b>	88	<b>97</b>

Ak=amikacin; Cpe=cefepime; Cax=ceftriaxone; Lvx=levofloxacin; Mer=meropenem; PT= piperacillin-tazobactam; Tig=tigecycline.

**Conclusions:** In 2004-2010 ESBL+ *E. coli* and *K. pneumoniae* were <90% susceptible to all study drugs except meropenem and tigecycline. ESBL+ *E. coli* were less susceptible to levofloxacin than ESBL+ *K. pneumoniae* perhaps reflecting the emergence of the CTX M-14/15 beta-lactamase. ESBL- isolates of both species remain susceptible to most studied agents with >85% susceptibilities. The increasing prevalence of resistant *E. coli* and *K. pneumoniae* requires continued monitoring in pediatric populations.

## Introduction

*Escherichia coli* and *Klebsiella pneumoniae* are important pathogens in pediatric patients accounting for 80% of all urinary tract infections, 20% of bloodstream infections, and as much as 30% of all hospital-associated infections [1, 2]. There has been a disturbing increase in resistance in *E. coli* and *K. pneumoniae* in the past decade due primarily to the emergence of extended-spectrum beta-lactamase (ESBL) producing strains [3, 4]. Even therapy with fluoroquinolones has been further compromised with the co-resistant *qnr* gene in these species [5]. Clinicians are struggling to keep pace with ever dwindling therapeutic choices available. This study looks at the susceptibility of *E. coli* and *K. pneumoniae* to a number of antimicrobial agents in a global pediatric population since 2004. This study is part of the larger ongoing Tigecycline Evaluation and Surveillance Trial.

## Materials & Methods

- ❖ **Clinical isolates:** Isolates were identified to the species level and tested at each participating laboratory. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria. All isolates were from pediatric patients (ages  $\leq 1$  to 16 years) with only one isolate per patient accepted. Isolates were collected during the years 2004 - 2010 from 1739 cumulative sites in 60 global countries.
- ❖ **Susceptibility testing:** Minimum inhibitory concentrations (MICs) were determined using broth microdilution plates manufactured by MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) and TREK Diagnostics (TREK Diagnostic Systems, Cleveland, OH, USA), following manufacturer and Clinical and Laboratory Standards Institute (CLSI) instructions for broth microdilution testing [6]. Susceptibility was determined using clinical breakpoints published by the CLSI [7] and the FDA (tigecycline) [8].
- ❖ **Quality Control:** QC of broth microdilution panels followed manufacturers' and CLSI guidelines using the following ATCC strains as needed and applicable: *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, and *Klebsiella pneumoniae* ATCC 700603 as ESBL-positive control.

## References

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## Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Surveillance Trial program group. This study was sponsored by Pfizer Inc.

## Results

Figure 1. Distribution of 5,026 *E. coli* and *K. pneumoniae* by specimen source from pediatric patients ( $\leq 1$  to 16 years), 2004 – 2010.

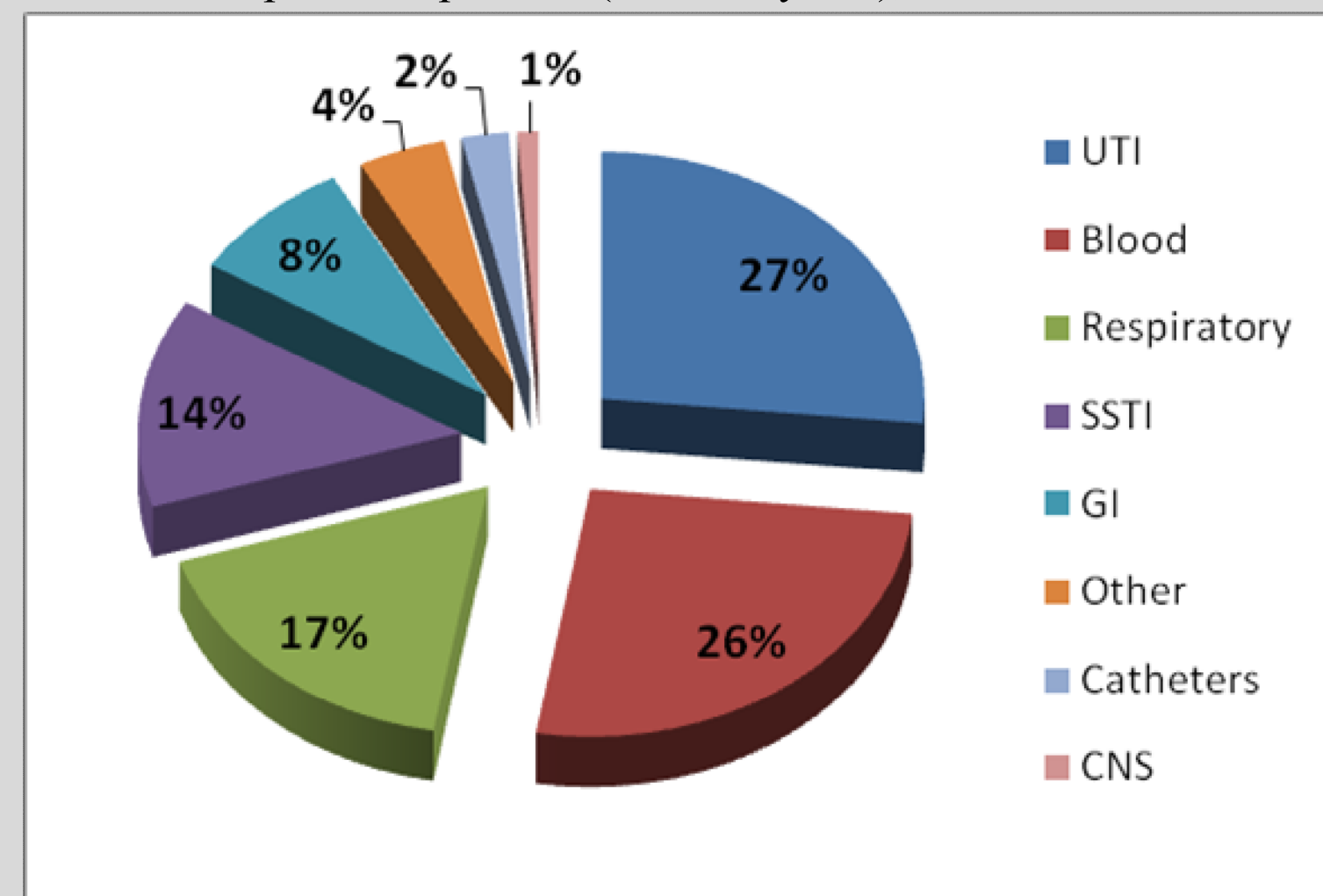


Figure 3. ESBL+ rate by specimen source for 810 ESBL+ *E. coli* and *K. pneumoniae* in pediatric patients ( $\leq 1$  to 16 years), 2004 – 2010.

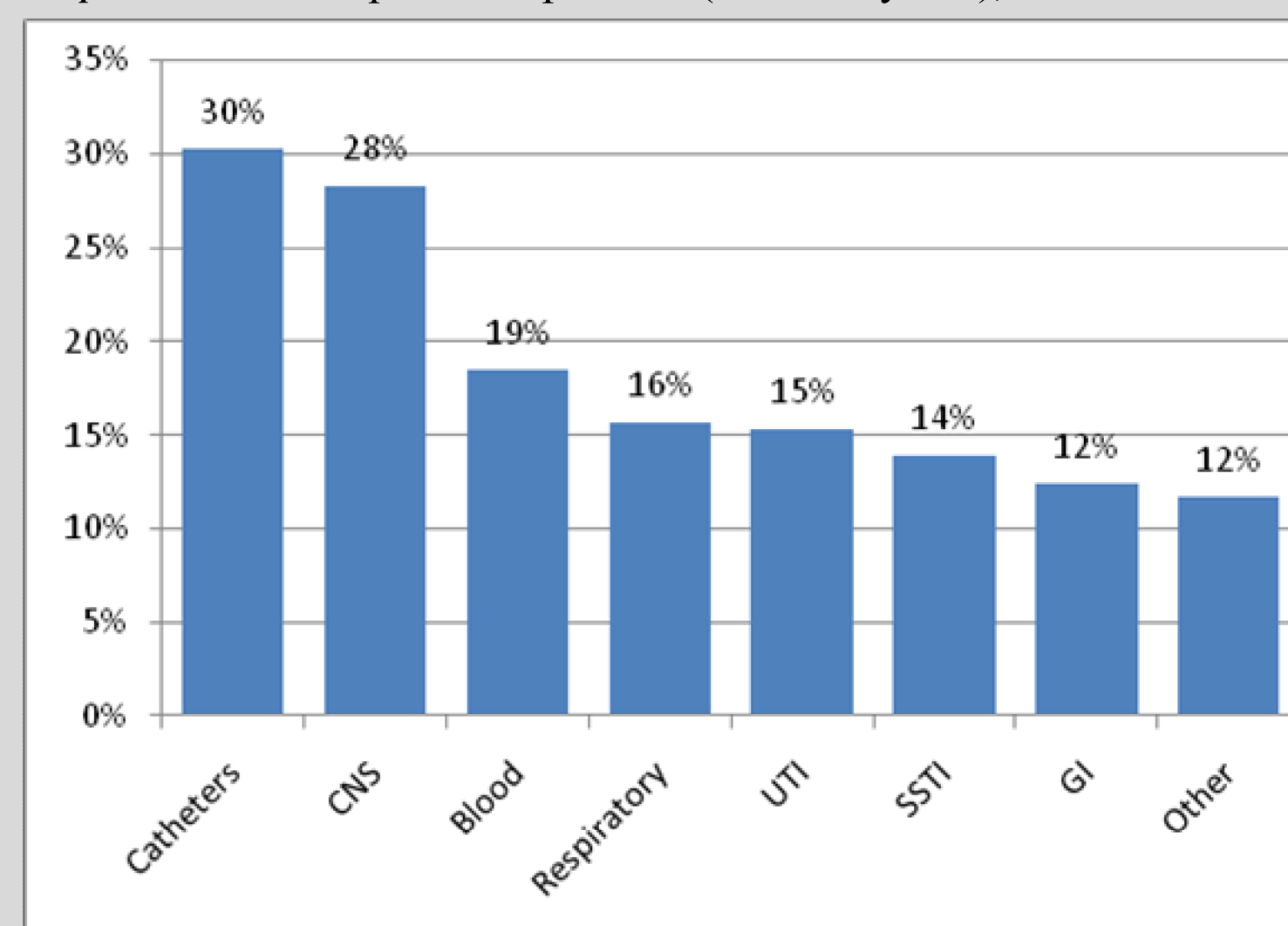


Table 1. *In vitro* susceptibility for tigecycline and comparators against *E. coli* and *K. pneumoniae* from pediatric patients ( $\leq 1$  to 16 years), 2004 – 2010.

Organism	Drug	(mcg/ml)		% Sus*	% Int	% Res
		MIC <sub>50</sub>	MIC <sub>90</sub>			
<i>Escherichia coli</i> n=2752	Tigecycline	0.12	0.5	99.9	0.1	0
	Amikacin	2	8	97.4	1.1	1.5
	Cefepime	$\leq 0.5$	8	91.3	2.1	6.6
	Ceftriaxone	$\leq 0.06$	64	82.7	1	16.3
	Levofloxacin	0.03	>8	80.6	1.2	18.2
	Meropenem	$\leq 0.06$	$\leq 0.06$	98.8	0.5	0.7
	Pip-Tazo	1	16	92.5	3.7	3.8
	<i>E. coli</i> , ESBL+ n=291	Tigecycline	0.25	0.5	99.7	0.3
Amikacin		4	32	85.2	6.5	8.3
Cefepime		16	>32	39.5	12.7	47.8
Ceftriaxone		>64	>64	2.4	2.4	95.2
Levofloxacin		8	>8	39.9	3.8	56.4
Meropenem		$\leq 0.06$	0.12	97.4	1.3	1.3
Pip-Tazo		4	128	76.3	13.1	10.7
<i>E. coli</i> , ESBL- n=2461		Tigecycline	0.12	0.5	100	0
	Amikacin	2	4	98.9	0.4	0.7
	Cefepime	$\leq 0.5$	1	97.4	0.9	1.8
	Ceftriaxone	$\leq 0.06$	0.5	92.2	0.8	7
	Levofloxacin	0.03	8	85.4	0.9	13.7
	Meropenem	$\leq 0.06$	$\leq 0.06$	99	0.4	0.6
	Pip-Tazo	1	8	94.4	2.6	3
	<i>Klebsiella pneumoniae</i> n=2274	Tigecycline	0.5	2	96.5	2.7
Amikacin		2	16	91.7	2.3	6
Cefepime		$\leq 0.5$	>32	82	3.1	14.9
Ceftriaxone		$\leq 0.06$	>64	66.8	1.5	31.7
Levofloxacin		0.06	8	87.7	2.2	10.1
Meropenem		$\leq 0.06$	0.12	96.1	0.8	3.1
Pip-Tazo		4	>128	79.6	6.5	13.9
<i>K. pneumoniae</i> , ESBL+ n=519		Tigecycline	0.5	2	94.8	4.1
	Amikacin	8	>64	75.7	5.8	18.5
	Cefepime	16	>32	42.2	8.5	49.3
	Ceftriaxone	>64	>64	1.2	1.7	97.1
	Levofloxacin	0.25	>8	72.6	3.9	23.5
	Meropenem	$\leq 0.06$	1	90.9	2.3	6.8
	Pip-Tazo	16	>128	51.8	15.2	33
	<i>K. pneumoniae</i> , ESBL- n=1755	Tigecycline	0.5	1	97	2.3
Amikacin		1	4	96.4	1.3	2.3
Cefepime		$\leq 0.5$	2	93.8	1.5	4.7
Ceftriaxone		$\leq 0.06$	8	86.3	1.4	12.3
Levofloxacin		0.06	1	92.2	1.7	6.2
Meropenem		$\leq 0.06$	0.12	97.7	0.4	1.9
Pip-Tazo		2	64	87.9	3.9	8.2

\* Interpretive criteria defined by CLSI document M100-S21 (2011), where breakpoints were available; tigecycline breakpoints defined by the FDA (Tygacil®, 2010).

Figure 2. Distribution of 5,026 *E. coli* and *K. pneumoniae* by collection location from pediatric patients, 2004 – 2010.

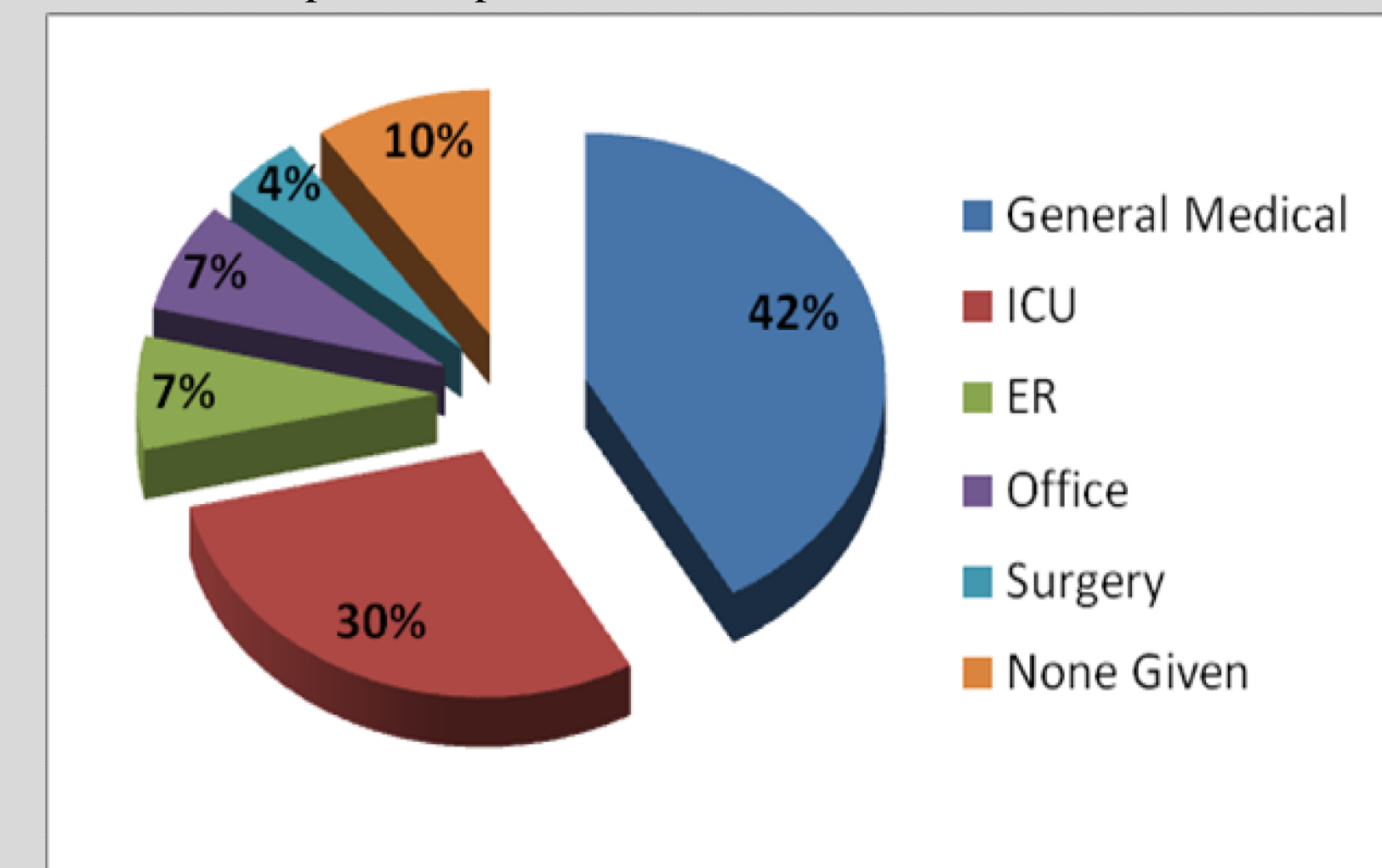
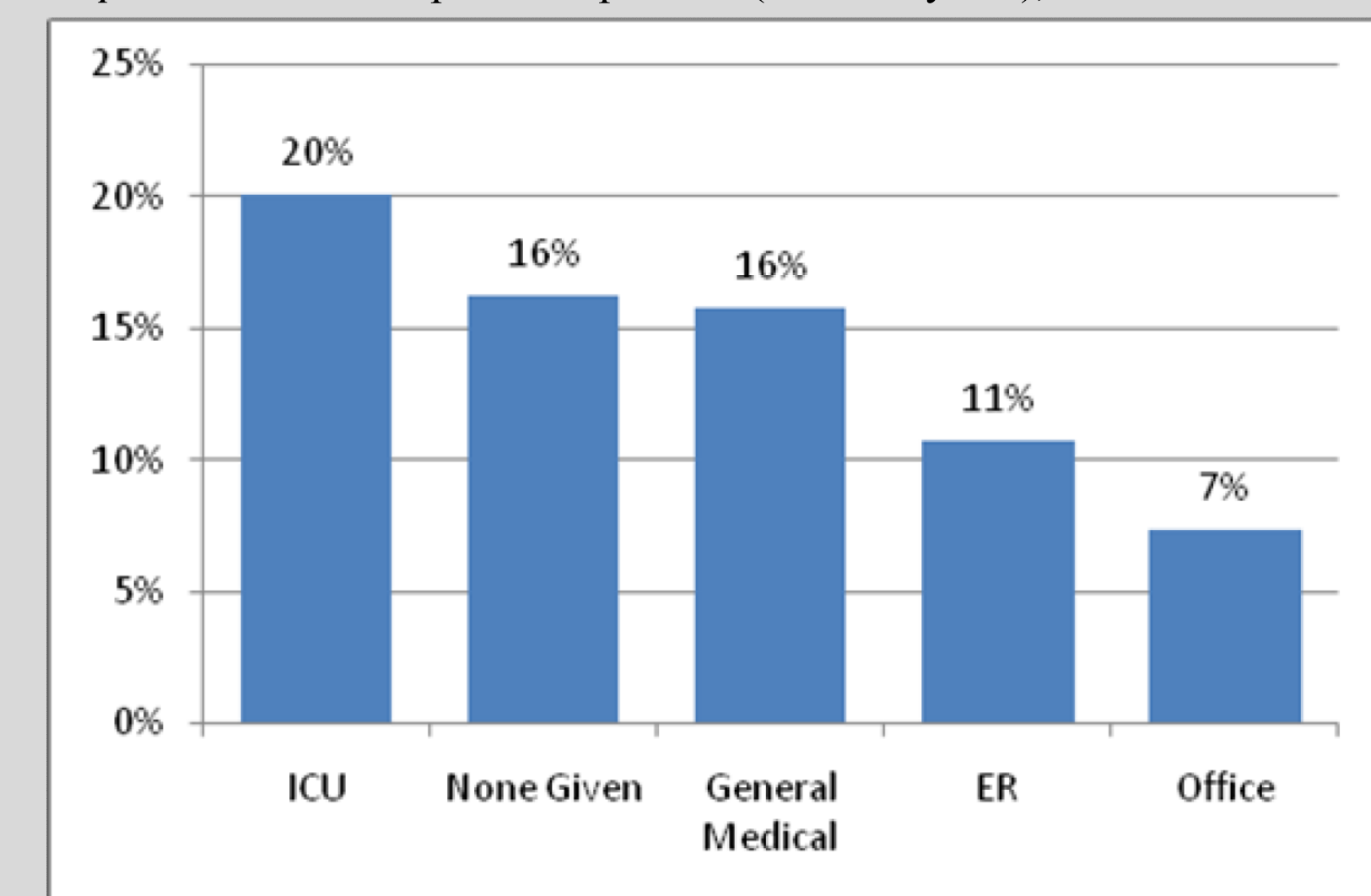


Figure 4. ESBL+ rate by collection location for 810 ESBL+ *E. coli* and *K. pneumoniae* from pediatric patients ( $\leq 1$  to 16 years), 2004 – 2010.



## Conclusions

- ❖ Tigecycline, amikacin, and meropenem were the most active antimicrobial agents *in vitro* against the pathogens *E. coli* and *K. pneumoniae* from a global pediatric population with >90% susceptible against both species. Only tigecycline and meropenem demonstrated >90% susceptibility against ESBL+ *E. coli* and *K. pneumoniae*.
- ❖ More than 50% of *E. coli* and *K. pneumoniae* came from urinary tract or blood stream sources; however, the highest percentage of ESBL+ isolates were seen in specimens from catheters and central nervous system sources. The majority of these two pediatric pathogens (72%) were from hospitalized patients with slightly more from the general medical units (42%) compared to intensive care units (30%). The percentage of ESBL+ isolates in hospitalized children (16% – 20%) was about double that seen in community-associated isolates (7% – 11%).
- ❖ The high incidence of ESBL+ *E. coli* and *K. pneumoniae* in pediatric populations globally limits empiric therapy to few antimicrobial agents. ESBL screening and confirmation is critical to successful therapy of these difficult to treat pathogens. The increasing prevalence of resistant *E. coli* and *K. pneumoniae* requires continued monitoring in pediatric populations. Further long term surveillance is warranted.