The Predictive Utility of Screening ESBL Swabs in Selecting Empiric Antibiotics for Gram Negative Sterile-Site Infections

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Abstract

Background: Extended-spectrum beta-lactamase (ESBL) screening swabs are performed widely as a means of identifying ESBL carriers and preventing transmission. We tested whether these results could have unintended benefits in predicting the ESBL status of subsequent infections with *E. coli* and *Klebsiella* spp. experienced by these patients.

Methods: A retrospective cohort study was conducted using an auto-populated antimicrobial stewardship database. Patients were included if 18 years of age or older, admitted to hospital between 2010 and 2015, and screened for ESBL prior to developing an *E. coli* or *Klebsiella* spp. sterile-site infection Test characteristics were derived using the screening swab ESBL result as test variable predicting the presence or absence of ESBL in the sterile site *Enterobacteriaceae* species.

Results: 2254 patients had sterile cultures positive for *E. coli* or *Klebsiella* spp. during the study period, and a total of 73/2254 patients had prior screening for ESBL (3%). Within this sample population a total of 27/73 screening swabs were positive for ESBL (37%), and a total of 28/73 sterile cultures were positive for ESBL (38%). The overall specificity of ESBL swabs was 89% (75%-96%) and the overall sensitivity was 79% (59%-91%). The positive predictive value was 81% (61%-93%) and the negative predictive value was 87% (73%-95%). The positive likelihood ratio was 7 (3-17) and the negative likelihood ratio was 0.24 (0.12-0.49). In the United States, where the prevalence of ESBL among *Enterobacteriaceae* sterile isolates is as high as 0.23, a positive ESBL screening swab would yield a post-test probability of 0.68 of third-generation cephalosporin resistance and a negative swab would yield a post-test probability of 0.067 (based on the derived likelihood ratios).

Conclusion: Prior ESBL screening swab results are a useful tool for predicting ESBL status of sterile site *E. coli* and *Klebsiella* spp. infections. The results of this study suggest that those with a positive ESBL screening swab should receive empiric carbapenem therapy for positive *E. coli* and *Klebsiella* spp. sterile cultures. Patients with negative ESBL screening swabs that are not critically ill may be treated with a carbapenem-sparing empiric regimen while awaiting sensitivity results.

Background

- ❑ *E. coli* and *Klebsiella spp.* among top causes of bloodstream infection, intra-abdominal sepsis, and SSI[1,2].
- ❑ ESBL infection associated with higher mortality, related to inadequate empiric antibiotic treatment[3-11].
- ❑ Screening swabs for AROs attractive for predicting resistance: widely used, drawn early.
- ❑ MRSA screening swabs have high Sp for predicting MRSA in subsequent *Staphylococcal* isolates[6,12].
- ❑ Hypothesis for ESBL: Positive screening ESBL swabs will reliably predict *Escherichia* and *Klebsiella* sterile culture resistance to third generation cephalosporins.

Methods

Study Design and Patient Selection:
- ❑ Retrospective cohort study from single center in Toronto over 5 years.
- ❑ All patients with positive sterile isolates for *Escherichia* or *Klebsiella* spp. and prior screening for ESBL.

Data Sources:
- ❑ Data derived from pre-existing auto-populated database.

ESBL screening protocols and methods:
- ❑ Rectal swab for ESBL on admission for known postive ESBL in past, healthcare in high-risk area, transfer to ICU, or for outbreak.
- ❑ ESBL assessed with culture on cefpodoxime-impregnated MacConkey agar for 48 hours and confirmed with B LACTA (Bio-Rad) and with double disc diffusion testing.

***E. coli* and *Klebsiella* spp. sterile isolate protocols:**
- ❑ Gram negative identified by morphology and species derived using MALDI-TOF (Vitek, bioMérieux).
- ❑ Susceptibilities performed using double disc diffusion testing on overnight culture.

Covariates:
- ❑ Age, sex, ward, service, sterile site, species, swab-culture duration extracted from database.

Statistical Analysis:
- ❑ Test characteristics derived from data. Confidence intervals calculated using the efficient-score method.
- ❑ Sub-group analysis by time: 'Immediate' – 0 to 48 hours, 'Recent' – 48 hours to 14 days, 'Remote' – greater than 14 days.

Regional ESBL-Producing Bacteria Prevalence and Calculated Post-Test Probability:
- ❑ Probability of ESBL among *E. coli* and *Klebsiella spp.* sterile site infections, given prior positive and negative ESBL screening, calculated from published prevalence data and study test characteristics. Scatter plot made using Stata 14.1 (Statacorp).

Results

Table 1. Baseline characteristics of 73 patients with sterile isolates that tested positive for *E. coli* or *Klebsiella spp.* and had prior screening for ESBL.

Variable		No. (%) of patients
	Age, yr, mean ± SD	65 ± 17
Sex	Male	53 (73)
	Female	20 (27)
Screening Result for ESBL	Positive	27 (37)
	Negative	46 (63)
ESBL Resistance of Gram Negative Sterile Isolates	Positive	28 (38)
	Negative	45 (62)
Gram Negative Sterile Isolates Species	*E. coli*	44 (60)
	Klebsiella spp.	29 (40)
Admission Type	Medical	43 (59)
	Surgical	28 (38)
	N/A	2 (3)
	Admitted to intensive care unit	25 (34)
	Swab and isolate collection performed on same admission	37 (51)
Sterile Cultures by Site	Blood	59 (81)
	Fluid	14 (19)
Time Between Swab and Isolate Collection	Immediate (< 48 h)	13 (18)
	Recent (48 h to 14 d)	12 (16)
	Remote (> 14 d)	48 (66)
	Time from swab to isolate collection, d, median (IQR)	27 (4 - 85)

Table 2. Test characteristics of the prediction of ESBL resistance among sterile clinical isolates of *E. coli* and *Klebsiella* spp. using prior screening swabs. Overall results included, along with stratification by time between screening swab and isolate collection.

Characteristic	Overall	Immediate	Recent	Remote
True Positives	22	5	4	13
True Negatives	40	8	7	25
False Positives	5	0	1	4
False Negatives	6	0	0	6
Sn, % (95% CI)	79 (59-91)	100 (46-100)	100 (40-100)	68 (43-86)
Sp, % (95% CI)	89 (75-96)	100 (60-100)	88 (47-99)	86 (67-95)
PPV, % (95% CI)	81 (61-93)	100 (46-100)	80 (30-99)	76 (50-92)
NPV, % (95% CI)	87 (73-95)	100 (60-100)	100 (56-100)	81 (62-92)
PLR (95% CI)	7.1 (3-17)	Infinity (N/A)	8.0 (1.3-50)	5.0 (1.9-13)
NLR (95% CI)	0.24 (0.12-0.49)	0 (N/A)	0 (N/A)	0.37 (0.19-0.72)

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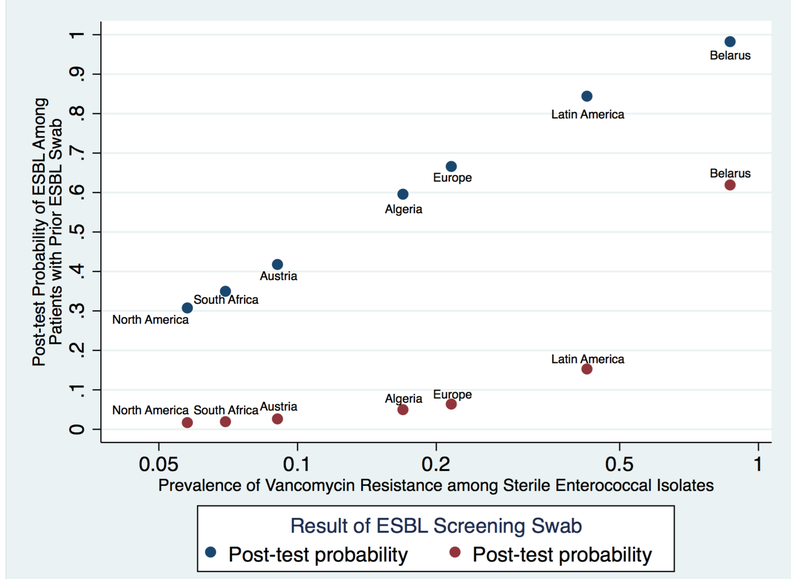
Figure 1. The Post-Test Probability of ESBL Among Patients with *E. coli* or *Klebsiella spp.* Sterile Site Infection and a Prior History of an ESBL Swab, as a Function of Differences in Regional Prevalence of ESBL. Each point represents published data on the regional prevalence of ESBL among sterile isolates of *E. coli* and *Klebsiella* and the calculated post-test probability using the test characteristics derived in the study.



Discussion

- ❑ First to demonstrate that a positive ESBL screening swab suggests that ESBL is highly probable *in E. coli* and *Klebsiella* spp. sterile culture isolates and necessitates empiric coverage while awaiting definitive susceptibility testing.
- ❑ In general, patients with negative ESBL swabs do not need carbapenems while awaiting antimicrobial sensitivity testing.
- ❑ Previous studies involved high-risk clinical settings and did not look at ESBL-production as a proportion of all *E. coli* and *Klebsiella spp.* sterile site infections[13-15].
- ❑ Consistent with long duration of rectal carriage of ESBL-producing bacteria, potential to acquire ESBL-producing bacteria with repeated healthcare exposure, and colonization as intermediate step towards infection with ESBL-producing bacteria[16].
- ❑ Post-test probability of ESBL sterile-site infection demonstrates exquisite sensitivity to slight increases in the prevalence of ESBL in *E. coli* and *Klebsiella* sterile culture isolates.
- ❑ Limitations relate to assumption of accurate cultures obtained in all sterile site infections, single-center design and small sample size.
- ❑ High possibility of ESBL in most regions with positive screening swab and *E. coli* or *Klebsiella* spp. sterile isolate necessitates effective empiric coverage with carbapenem.
- ❑ In high-risk populations and high suspicion for ESBL infection, must add antibiotics effective against ESBL-producing bacteria if positive ESBL screening swab, even before positive sterile culture.