The Effect of Infection Precautions on Colonization of Nursing Staff with Extended Spectrum Beta-Lactamase Producing Enterobacteriaceae in Three Beirut Hospitals

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Research

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Abstract

Background: ESBL-PE are emerging worldwide. This study assesses the effect of contact precaution (CP) on ESBL-PE-colonization rates among nurses in 3 hospitals in Beirut, where ESBL is endemic, to define risk factors for colonization, and evaluate the ongoing use of CP to prevent ESBL-PE transmission to healthy nurses.

Methods: Cross-sectional, non-randomized study completed in three hospitals. Hospital 1 required CP, Hospital 2 recently stopped CP, and Hospital 3 had stopped it 3 years previously. Questionnaires and stool-collection containers were distributed to all patient care nurses in those 3 hospitals. Returned samples were tested using agar dilution technique.

Results: 269 of 733 nurses volunteered; 140 met inclusion criteria (no recent hospitalization, antibiotic use, known ESBL-PE colonization). 15% were ESBL-positive. Compared to nurses from Hospital 3, nurses from Hospital 1 were 59% less likely to be colonized, while nurses from Hospital 2 were 62% more likely to be colonized.

Discussion: In hospitals where CP is ongoing for ESBL-positive patients, transmission to nursing staff was reduced. Additionally, a work experience of 2-4 years increased the odds of ESBL-PE colonization in comparison with longer nursing experience.

HIGHLIGHTS :

• We examined the impact of contact precautions (CP) for Extended spectrum beta-lactamase- producing Enterobacteriaceae (ESBL-PE) colonized patients on rates of ESBL-PE colonization in nursing staff.

• We found significantly decreased rates of colonization in nurses from a hospital utilizing CP, and significantly increased rates of colonization among nurses from a hospital that recently

• discontinued CP, compared with nurses from a hospital that had discontinued CP 3 years previously.

• Findings suggest that contact precaution may be required to prevent ESBL-PE transmission from patients to nursing staff.

Introduction

Extended spectrum ß-lactamase-producing Enterobacteriaceae (ESBL-PE) are classified as multidrug-resistant organisms (MDROs) by the Center for Disease Control and Prevention (CDC). These organisms can cause several diseases including urinary tract infections1 and pneumonia2 and may lead to serious outcomes such as bacteremia and sepsis that are difficult to treat due to paucity of available antibiotic options. This can result in prolonged hospitalizations, and an increase in mortality and health care cost3-5.

Intestinal colonization has been shown to be the site of carriage of ESBL-PE6. The mechanism of person-to-person transmission is via contact with a colonized environment or patient body part. Within the bacterial milieu, resistance is transmitted through genes located on self- transmissible plasmids that can circulate amongst bacterial species7. In the hospital setting, cross-contamination of Gram-negative bacteria via hands of healthcare workers (HCWs) to patients occurs primarily due to inadequate hand hygiene8.

In a study by Barreto Miranda et al., the median duration of colonization of ESBL-producing Escherichia coli (E. coli) in the human body after exposure is at least six months, and the persistence of colonization depended on multiple factors, such as bacterial genetic factors and patient lifestyle9. Efforts to eradicate intestinal carriage did not result in long term effects in achieving this goal. Thus, the gastrointestinal tract serves as a reservoir for further transmission. This cycle of transmission is compounded by persistence of ESBL producers in the environment of care. These MDROs can also survive on surfaces for many months if disinfection is not appropriately performed10.

Infection control practices specific for MDROs transmission are followed in acute-care hospitals (and sometimes in long-term care settings) for patients colonized or infected with ESBL-PE according to Center for Disease Control and Prevention (CDC) recommendations11. These practices fall under two broad categories, administrative such as compliance with contact precaution (CP), and clinical such as hand hygiene, type of infection precaution, appropriate use of antibiotics, active screening, surveillance cultures, dedication of isolated rooms or appropriate distance of isolation between beds in shared rooms, enhanced environmental cleaning, education of health care personnel, and communication about isolated patients CP11. However, in environments with high MDROs prevalence in and outside of healthcare settings, the utility of CP is questionable12. Despite the support of the use of CP for ESBL-PE-colonized patients in healthcare settings11,13, more recent studies do question its efficacy, and some are providing data in support of lack of benefit12,14.

Risk factors for colonization are well described in the literature. One of the most important of those factors is recent antibiotic use (during the preceding 4 to 12 months)15,16. Any use of antibiotics can increase the emergence of resistance. In countries (such as Lebanon) where resources are available, but where regulatory healthcare policy is not enforced, widespread misuse and overuse of antimicrobials occur with the significant consequence of fostering microbial resistance16-18. Along those same lines, unregulated and improper utilization of antibiotics in livestock and agriculture may lead to the transmission of resistant strains to humans19,20.

Other risk for MDROs transmission includes previous hospitalization21 as well as household contact with patients who are known to be ESBL-PE-colonized or ESBL-PE-infected22, use of

antacids23, diabetes mellitus21, dialysis, and residence in long-term care facilities or nursing homes24. Gender and age may also play a role as well, but data are inconclusive.

This classical risk of nosocomial ESBL-producer acquisition is compounded by its rapid worldwide emergence in environmental samples unrelated to health care25-27, such as animal cultures28,29, food sources30-36, surface water (in Lebanon after the arrival of refugees)37,38, and travel history to endemic areas9,39.

Several international studies have evaluated fecal carriage of ESBL-producing isolates from the stools of healthy non-hospitalized individuals15,40 with a prevalence of up to 14% in one study15. However, few data are available about the prevalence of ESBL-PE in HCWs41-43. Application of CP is certainly a cumbersome practice, with several practical and economical disadvantages, as well as adverse psychological effects on the isolated patient5. Hence, if it is also ineffective, then eliminating it in healthcare facilities would be comprehensibly justifiable44. Moreover, in the new era of SARS-CoV2 transmission and the worldwide shortage of personal protective equipment (PPE), making more PPE available for a higher acuity and severity disease would certainly be critical in many care settings.

Most of the rationale behind the use of CP in preventing the transmission of ESBL-producers is deduced from literature supporting its utility with methicillin-resistant Staphylococcus aureus45.
Recommendations regarding the role of contact isolation in preventing the transmission of ESBL-producers particularly in outbreak settings are proven46-48. However, its utility in settings where HCWs have a high risk of colonization is not well-studied

The primary objective of this study was to determine if CP are associated with reduced rates of ESBL-PE colonization in nursing staff. The secondary objective was to identify additional risk factors for ESBL-PE colonization among nursing staff.

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Participants

Study participants were nurses recruited between July and November 2017 from three hospitals located in the greater Beirut area, with similar patient profiles and a comparable size of employees. Hospital 1 required contact isolation for ESBL-carriers, Hospital 2 had recently stopped this practice, and Hospital 3 had stopped isolation for ESBL-carriers three years prior to the study period.

All nurses on staff at the 3 participating hospitals were initially eligible. The final sample of those who volunteered for the study excluded those nurses who had themselves been hospitalized for more than 2 days within the past 12 months, nurses already known to be colonized with ESBL-PE or who had contact with any household members known to be ESBL- positive, and those with any utilization of an antimicrobial agent (any class, any agent) within the preceding 4 months.

Procedure and Measures

Prior to initiation of enrolment and data collection, the study was presented to the nursing leadership in each of the three hospitals to explain the study, and to encourage and support maximal nursing staff

participation. Ethical conduct of research was strictly followed in every step, explaining the study objectively, sharing the methodology clearly via written material, promoting it on each floor via flyers written in clear, understandable instructions, and preserving the confidentiality of results. A numbered sterile cup for a stool sample and a questionnaire with the same number were placed together in a plastic bag and distributed to all nursing staff, through the nursing supervisor of each nursing unit.

Questionnaires collected the following information: patient's age and gender, length of time working as a clinical nurse, clinical setting of work over the preceding 6 months, hospitalizations within the preceding 12 months, antibiotic treatment during the preceding 4 months, personal colonization status by ESBL-PE if known, and contact with household members whose colonization status was known to be positive for ESBL-PE.

The questionnaire was completed at home by the volunteering participants and returned with the stool specimen. Fresh stool samples were returned to the lab of each hospital where they were stored at 4 degrees centigrade. The samples were retrieved within 24 hours, and the questionnaire was reviewed. If there were no exclusion criteria based on the questionnaire, the samples were transported to a single laboratory for processing to ensure standardized results.

Stool samples were inoculated on a MacConkey agar plate and incubated at 37°C for 24 hours. Lactose fermenter colonies (E. coli, Klebsiella spp., Citrobacter spp., Enterobacter spp.) were picked and suspended in a sterile normal saline solution to make a 0.5 Macfarland bacterial

suspension. Using a cotton swab, the bacterial suspension was evenly and uniformly streaked on a Mueller-Hinton agar plate. A ceftazidime disk (30 mcg), a cefotaxime disk (30 mcg) and a cefepime disk (30 mcg) were placed around an amoxicillin-clavulanic acid disk (20-10 mcg) located in the center of the plate and then incubated at 37°C for 24 hours. The presence of a bacterial inhibition area between the oxyimino cephalosporin disks and the amoxicillin- clavulanic acid disk was considered a positive test result. The cause of this inhibition area is the synergism between the oxyimino cephalosporins and the clavulanic acid in deactivating the extended-spectrum beta-lactamases secreted by the bacteria. Bacteria that were resistant to oxyimino cephalosporins (according to the disk diffusion method, CLSI Document M100–S19) and showed synergism with clavulanic acid were identified as ESBL positive bacteria.

Approvals and Oversight

Administrative support and informed consent from the leaderships in each hospital were secured via full disclosure of all details, and by ascertaining the anonymity of the hospital and staff members along the course of the study and after the results were analyzed. Individual verbal consent was also obtained from each participating nurse, who had the opportunity to ask any question about the study, which were answered by the primary investigator.

Results from nurses' stool cultures were confidential. They were made available solely to each individual nurse by e-mail or phone messages, and were not shared otherwise, namely other hospital staff,

administration and each individual hospital's infection control departments.

Education to each of the recipients of those results as to what they meant was provided upon request.

Data Analysis

Based on Bassyouni et al.51, we fixed our expected frequency of prevalence of ESBL-PE colonization at 21% and our precision level at +/- 5%, thus we obtained a minimum sample size of 255 for a confidence level of 95% to detect rate differences between the 3 hospitals.

All statistical analyses were carried out using SPSS software (IBM SPSS Statistics, version 21; IBM, Armonk, NY, USA). We performed descriptive statistics reporting means (±standard deviations) for continuous variables and frequencies (percentages) for categorical ones. All factors potentially associated with ESBL-PE colonization, including hospital type, were first analyzed using bivariate statistics (Student's t-test for continuous variables and Pearson's Chi- square or Fisher's exact test for categorical variables). To assess the independent effect of hospital type, we performed binary logistic regression using a generalized estimating equation model to account for correlation between measures taken from the same hospital with the culture result (ESBL-PE colonization) as the dependent variable and potential associated factors as covariates. We chose as covariates factors associated with the dependent variable with a p- value<0.2 in the bivariate analysis. Adjusted Odds Ratios (OR) and 95% confidence intervals (CI) were reported. For all analyses, a p-value <0.05 was considered statistically significant

Results

All 733 of the nurses at the three hospitals received questionnaires and containers, and a total of 269 nurses (36.7%) returned the questionnaire. Of the 269 samples, 129 (48%) were excluded based on exclusion criteria, as detailed in Figure 1. Thus, the final sample was comprised of 140 with complete questionnaire and stool sample data.

Figure 1: Flow diagram of study inclusion and exclusion criteria. The numbers do not total 129 as the exclusion criteria are not mutually exclusive.

Participant characteristics are detailed in Table 1 and Table 2. Approximately half were working in Hospital 1 (i.e., where contact isolation was practiced), more than two thirds were female, and the majority of respondents had more than 6 years of nursing experience.

Of the 140 cultures performed, 21 (15%) were positive. As shown in Figure 2, nurses working in Hospital 1 (isolation being followed) were significantly less colonized (p=0.016) than those working in Hospital 2 (recently stopped isolation) and Hospital 3 (no isolation for the prior 3 years).

Bivariate analyses for other factors associated with ESBL colonization are shown in Table 3. Nurses who were ESBL-colonized were significantly younger than nurses without ESBL- colonization. Nurses with less

than 4 years of clinical experience tended to be more colonized than other nurses but this difference did not reach statistical significance.

Figure 2: Percentage of positive cultures per hospital (N=140)

Finally, the multivariable analysis showed a significant association between Hospital type and ESBL-PE colonization after control for both age and seniority level, detailed in table 4. Compared to nurses working in a hospital with no isolation procedures the last 3 years, nurses working in a hospital with isolation required were 59% less likely to have a positive culture. Additionally, compared to nurses working in a hospital with no isolation procedures the last 3 years, nurses working in a hospital that recently discontinued isolation for ESBL-PE carriers were 62% more likely to have a positive culture. Finally, seniority remained significant in the model, with nurses with 2-4 years of experience 2.6 times more likely to have a positive culture than nurses who have worked more than 6 years.

Discussion:

This is the first study from Lebanon defining the prevalence and risk factors for ESBL-PE colonization in nursing staff in relation to different hospital infection control measures with ESBL-colonized and ESBL-infected patients.

Hospital 1, where contact isolation was still being performed, had the lowest prevalence rate of colonization in nursing staff. We believe that it was likely due to a favorable effect of CP. Surprisingly, Hospital 2, where CP was removed within the month preceding sample collection, had the highest prevalence of ESBL-PE colonization. Having found no explanation for this phenomenon in the literature, we propose a few possible reasons leading to this highest prevalence.

First, we theorize that this might likely be explainable by a ‘flooding' effect, whereby the gastrointestinal tracts of nursing staff were rather quickly populated by resistant organisms ‘new' to their systems after lifting CP. Second, it is possible that nursing staff may have felt more ‘secure' that isolation was no more required, and consequently less compliant with strict adherence to standard precautions, hence driving the rates of colonization to a high level. A

third possible explanation is that environmental contamination may play a significant role (e.g. phones, cart…)49-51, where ESBL-PE can survive on surfaces for many months if disinfection is not well performed10,52, leading to concerns about direct causality. Consequently, evaluating the environmental contamination and monitoring the cleaning process are critical53. Hence, upon discontinuation of CP for ESBL-PE colonized/infected patients in any healthcare organization, it is recommended to provide enhanced and ongoing education to staff about the need for compliance with standard precautions and monitoring of compliance48. This education should emphasize the critical need for compliance with hand hygiene, environmental cleaning and decontamination, ongoing surveillance, all in order to mitigate the potential for increased transmission. Furthermore, molecular typing of ESBL-PE from HCW may have a role in case of an outbreak, to investigate the source of acquisition, whether from the hospital or the

community, knowing that there may be differences within the community vs. hospital-acquired strains, whereby the community strains are less resistant48. However, this was not performed in our study due to lack of resources and since it was not part of the original study design.

A study conducted by Bassyouni et al. in Egypt in 2013, published in 2015, demonstrated that the rate of fecal carriage of ESBL-PE in HCW practicing standard precautions was 21%41, which is roughly comparable to what we found despite the smaller number of samples in our study.

In the current study, the highest rates of ESBL-PE colonization were in nurses with 2-4 years of clinical experience, especially compared to those who have worked much longer. Our interpretation of this observation is that less experienced nurses get colonized upon entering

the hospital environment, which is consistent with the 'flooding' effect described above, especially in settings were contact isolation is not performed. Similarly, the ESBL-PE prevalence data for nurses in hospitals that do not require CP in our study are comparable to the rates of colonized patients found in a retrospective study of 16 different Lebanese hospitals between January 2011 and December 2013, published in 2016 by the Lebanese Society of Infectious Diseases and Clinical Microbiology54, where ESBL-PE rate of E. coli isolates was 32.3% and that of Klebsiella was 29.2%.

On the other hand, we find a similarity between the prevalence data of the hospital still requiring CP to that of a Lebanese nursing home data55, which is lower than the hospital resistance data described above54. This is likely due to the nursing home prevalence being more reflective of community prevalence data as opposed to acute care hospital data. Hence, once again, we question the role of the hospital environmental contamination by hospital-acquired strains in regards to direct causality of the higher ESBL-PE rates upon discontinuation of CP. Accordingly, we suggest that hospital environmental sampling be examined as a possible additional reservoir in support of our theory regarding the efficacy of ongoing CP for ESBL-PE.

Hence, it is certainly not surprising to unveil a high rate of colonization of ESBL producers in the Lebanese community, of which nurses are an integral part. This is where the dissection of the sources of ESBL, whether community- or nosocomially-acquired, becomes a question that can be answered neither microbiologically nor epidemiologically, at this point and with the current resources in the country.

Notwithstanding complexity and variability of data collection and methodologies used to assess resistance in the different studies, a study by Challita et al. completed during the second half of 2015 showed an ESBL E. coli prevalence of 7.7% in a Lebanese nursing home55. This is lower than hospital resistance data in the country, as detailed above. We are not able to justify this lower than average prevalence data point, especially in an elderly institutionalized cohort of patients. However, we do find a reflection of this prevalence in our nursing staff cohort of hospital 1, where CP continues to be practiced. Hence, we question whether the effect of health-care acquisition is mitigated by strict adherence to CP, ultimately resulting in a lower prevalence of ESBL Gram-negative colonization amongst nurses. Only 8.9%

were ESBL positive carriers in Hospital 1, and this was in agreement with the prevalence of ESBL E. coli in the Challita study (7.7%)55.

A study conducted by Hilty M et al. demonstrated that the contact isolation effect might be distinguishable between the clones of ESBL-PE22. One hypothesis explaining this observation is that there may be differences within community vs. hospital-acquired strains, such that the community strains are less resistant and may hence be more easily cleared by the gastrointestinal tract48. Based on our observation that showed a high colonization rate especially in the hospital where CP was recently removed and knowing the existence of the different strains, we do believe that CP imparts at least a partially protective effect on transmission of specific nosocomial strains of ESBL-PE to healthy nursing staff without being able to prove it in this study. To reduce the burden of this colonization, one promising approach

is fecal microbiota transplantation that may lead to ‘decolonization' of ESBL-PE from the GI tract of carriers. However, this theory needs further research.

Additionally, since ESBL-carrying organisms are spreading their resistance genes via plasmids, discovery of the "pCURE", targeting plasmids might be another promising approach for de- colonization without harming the normal flora in the colonized individual56. This would be particularly valuable in HCWs who may potentially spread it to their patients. However, further investigations are required concerning these innovations.

This study has several limitations. In the first place, the level of nursing staff participation was somewhat low (269 volunteered from a potential pool of 733 nurses) and participation was not congruous between the three hospitals. Our sample contained many more nurses from Hospital 1 (52.4% of our sample) compared to Hospital 2 (18.2%) and Hospital 3 (29.4%). We theorize that this higher rate of participation of Hospital 1 nursing staff is mainly fueled by an inherent interest to confirm that their laborious practices of donning gowns and gloves for each ESBL-PE patient encounter are indeed leading to a transmission protective effect both for them and for patients. Additionally, another unstated reason could be the ultimate possibility of discontinuing this practice if it were found to be ineffective. Finally, the overall low rate of participation could be due to needing to provide stool samples, which many people find uncomfortable. Despite the potential limitation of lower participation rates and unequal sample sizes, we were adequately powered, and our group differences were significant, revealing the

importance of CP as a protective way for curtaining transmission of ESBL-PE from patients to nursing staff.

Moreover, with our strict exclusion criteria, 33.1% of volunteers were excluded due to the recent intake of antibiotic within the preceding 4 months. The most commonly utilized antibiotics were amoxicillin-clavulanic acid (39%), multiple antibiotics (14.6%), cephalosporins (10%) and fluoroquinolones (10%). In a country like Lebanon, where medications such as antibiotics are purchased without a prescription,

such a high rate of antibiotic use may not be surprising although it is very disturbing, particularly in a relatively younger population and healthcare professionals. We suggest that the overly high use of amoxicillin-clavulanic acid is likely based on its low price, availability, and familiarity with its use57.

Another limitation of the current study was our inability to relate the prevalence of ESBL-PE in nurses with the clinical setting where most of the nurse's time was spent. Our initial intent was to attempt establishing some link with high-risk settings such as the emergency department and the Intensive Care Unit (higher risk of unprotected contact, exposure to wounds, trauma, etc.). However, the rates of response from the different settings were insufficient to permit examination of site-specific data.

Lastly, due to the lack of funding, we could not utilize PCR technology to analyze specific ESBL gene types in each hospital58. Such a tool would be highly recommended in studies like ours, in

order to determine the clonality of ESBL genes, which may explain certain epidemiologic trends (nosocomial vs. community strains, site-specificity, environmental acquisition, etc.).

Despite those limitations, we do believe this study provides an important confirmatory observation regarding the protective impact that CP have against transmission of ESBL-PE strains to nursing staff.

Conclusion:

Contact precautions do impart a positive impact on reducing the transmission risk of ESBL producing gram negatives to nursing staff. Risk factors for colonization were removal of CP (including recent discontinuation) and a clinical work experience of 2 to 4 years. Further studies are required to define the role of hospital environmental contamination vs. community contribution, and the roles of ESBL-PE clonality.

Abbreviations:

CP	**Contact Precautions**
E. coli	Escherichia coli
ESBL	Extended-Spectrum Beta-Lactamase
ESBL-PE	Extended-Spectrum Beta-Lactamase-producing Enterobacteriaceae
HCWs	Healthcare Workers
MDROs	Multidrug-Resistant Organisms
OR	Odds Ratio

Declaration

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval:

Ethics approval was secured from the nursing administration who endorsed this study and assisted in its execution and marketing to all nursing staff.

Data availability: The data sets utilized in this study, analyzed in this manuscript and presented in tables and graphs, are all available from the corresponding author on reasonable request.

Conflict of Interest:

All authors: no conflicts.

There were no financial nor non-financial competing interests in this study

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Tables

Table 1: Sample characteristics per hospital

	Hospital 1	Hospital 2	Hospital 3	p-value
	(n=136)	(n=49)	(n=77)	
Age, mean ± SD	37.9 ± 9.1	32.8 ± 7.5	33.3 ± 9.4	<0.001
Females, n (%)	94 (66.7)	36 (73.5)	56 (70.9)	0.623
Seniority level, n (%)				
< 2 years	22 (15.7)	5 (10.2)	12 (15.2)	0.674
2 - 4 years	10 (7.1)	5 (10.2)	11 (13.9)	
4 - 6 years	10 (7.1)	5 (10.2)	5 (6.3)	
> 6 years	98 (70.0)	34 (69.4)	51 (64.6)	

Table 2: Sample characteristics	
	All nurses (N=269)
Age (years)	
mean ± SD	35.6 ± 9.2
range	20-65
Female, n (%)	186 (69.1)
Hospital, n (%)	
1- Isolation	141 (52.4)
2- Recently discontinued isolation	49
3- No isolation in the previous 3 years	79
Seniority level, n (%)	
< 2 years	39
2 - 4 years	26 (9.7)
4 - 6 years	20 (7.5)
> 6 years	183 (68.3)
Clinical setting in the last 6 months	
Multiple floors	51
Medicine	64
Surgery	62
Critical care	56
Psychiatry	5
Interventional	26 (9.8)

Table 3: Characteristics of nurses (N=140) by culture result			
	Nurses **not** colonized with ESBL-PE (N=119)	Nurses colonized with ESBL-PE (N=21)	p-value
Age (years)			
mean ± SD	36.6 ± 8.4	31.0 ± 8.2	0.006
Gender, n (%)			
Female	82 (86.3)	13 (13.7)	0.526
Male	37 (82.2)	8 (17.8)	
Seniority level (years)			0.075
< 2 years	14 (73.7)	5 (26.3)	
2 - 4 years	8 (66.7)	4 (33.3)	
4 - 6 years	10 (90.9)	1 (9.1)	
> 6 years	87 (88.8)	11 (11.2)	
Clinical setting in the last 6 months			0.240
Multiple floors	24 (92.3)	2 (7.7)	
Medicine	26 (74.3)	9 (25.7)	
Surgery	28 (87.5)	4 (12.5)	
Critical care	25 (89.3)	3 (10.7)	
Psychiatry	1 (50.0)	1 (50.0)	
Interventional	12 (85.7)	2 (14.3)	

Figures

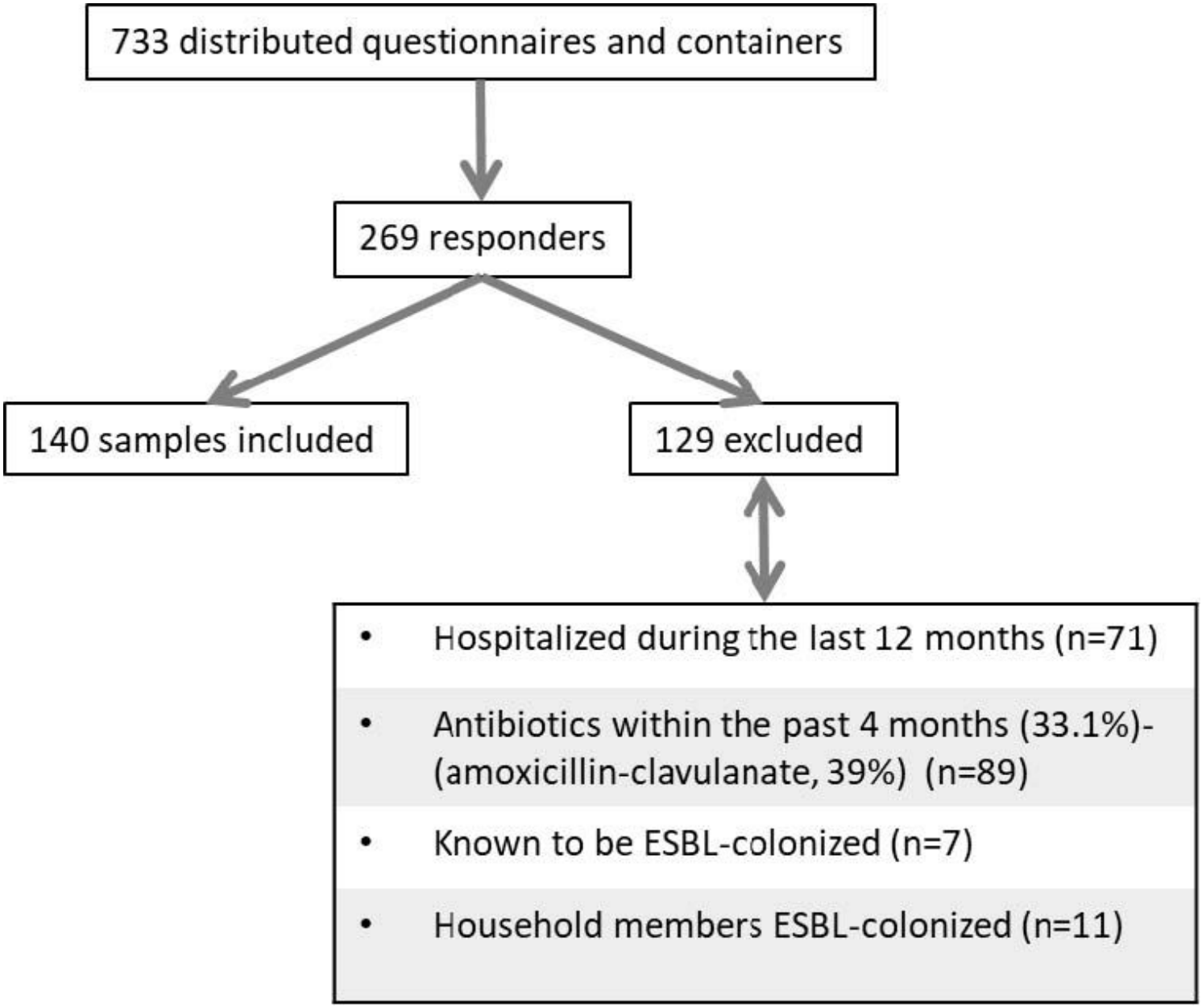

Figure 1

Flow diagram of study inclusion and exclusion criteria. The numbers do not total 129as the exclusion criteria are not mutually exclusive.

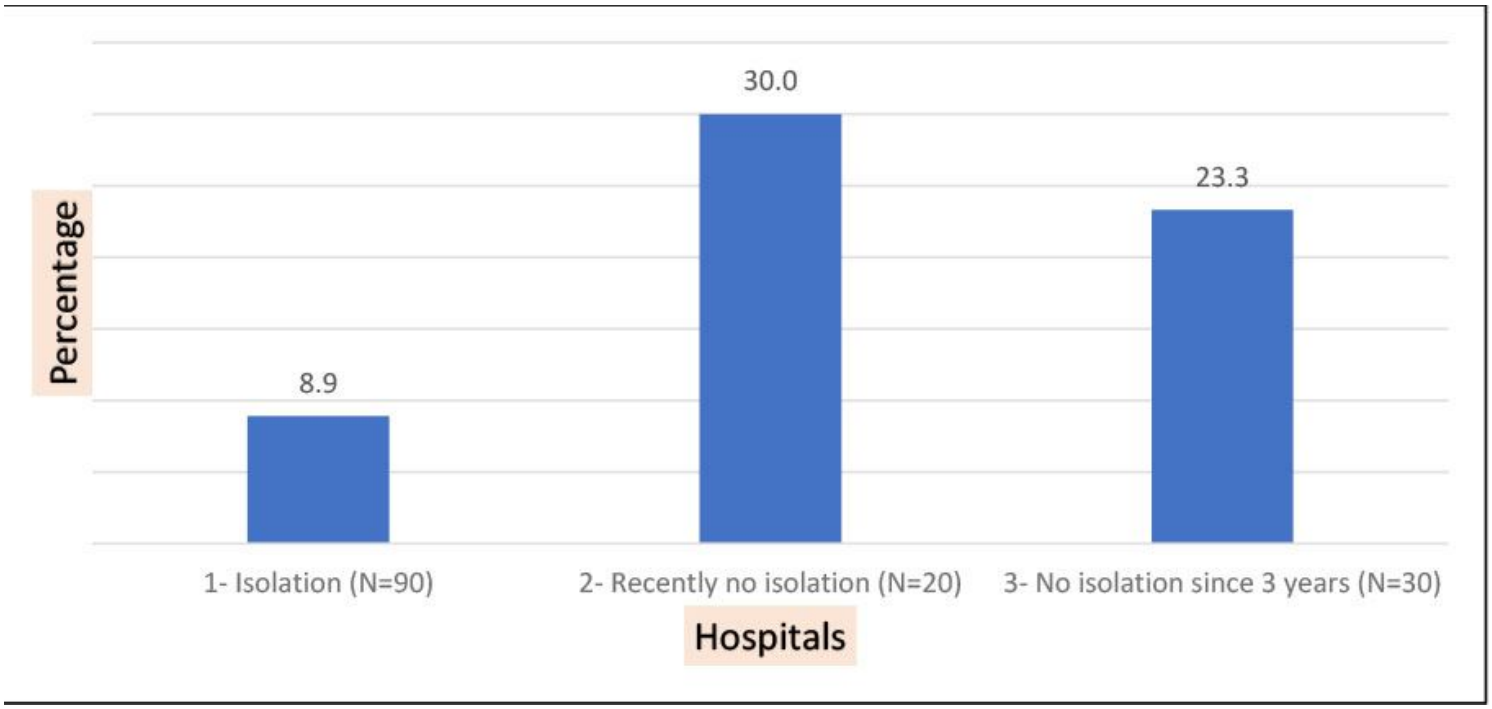

Figure 2

Percentage of positive cultures per hospital (N=140)