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Title: Antibiotic consumption and Enterobacteriaceae skin colonization in hospitalised adults

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Summary

Enterobacteriaceae are increasingly antibiotic resistant and skin colonization with Enterobacteriaceae may contribute to their spread in hospitals. We screened one hundred hospitalised adults for Enterobacteriaceae skin colonization and assessed potential risk factors, including antibiotic consumption. Multivariable analysis identified antibiotic consumption whilst an inpatient (odds ratio 3.16, 95% confidence interval 1.19 to 8.4) and being male (2.92, 1.06-8.4) were risk factors for Enterobacteriaceae skin colonization. These risk factors for Enterobacteriaceae skin colonization require confirmation. If these risk factors are confirmed, work to understand the biological mechanism involved may lead to the development of interventions to prevent Enterobacteriaceae skin colonization.

Keywords: Antibiotic, Colonization, Dermal, Enterobacteriaceae, Skin

Introduction

Enterobacteriaceae, including *Escherichia coli* and *Klebsiella pneumoniae*, are pathogens associated with significant mortality in hospitalised patients. Evidence suggests antibiotic treated hospitalised patients are at high risk of skin colonization with Enterobacteriaceae. One study in 1972 determined that 70% of hospitalised patients treated with antibiotics had *Klebsiella* skin colonization. This compared to 0% in those not treated with antibiotics.¹ Skin colonization is a potentially important route for the transmission of Enterobacteriaceae.² Transmission may occur by patient to patient spread and/or via the hands of healthcare workers. Skin colonization with Enterobacteriaceae may therefore contribute to outbreaks of antibiotic resistant Enterobacteriaceae in hospitals. Data implicating antibiotic use with Enterobacteriaceae skin colonization are old and it is uncertain how relevant the data remains. In view of the increasing healthcare threat posed by antibiotic resistant Enterobacteriaceae to hospitalised patients, we undertook a study of Enterobacteriaceae skin colonization to determine how common it is and if antibiotic use is a risk factor for Enterobacteriaceae skin colonization.

Methods

Study population: The study was a prospective cohort feasibility study. Adult patients admitted to medical and surgical wards at Leeds Teaching Hospitals NHS Trust with capacity to consent were eligible; those consuming antibiotics on admission to hospital or within one month prior to hospital admission were excluded. Included patients were sampled at single time points i.e. this was not a longitudinal study. Clinical data were collected on factors which were considered likely to impact on Enterobacteriaceae skin colonization including antibiotic use, see Table I.

Sample collection: Bacteria were isolated from patient's skin using dry cotton swabs which were transported in the manufacturer's transport media (Sterilin, M40 Transystem), between 9 am and 5 pm; no restrictions on personal hygiene were required prior to sampling. The following sites were

sampled: axilla, buttock, forearm-hand, groin and nose (intranasal). The duration of the swabbing procedure was not defined in the study protocol. Ethical approval was obtained from the Health Research Authority (158402) and patients provided informed consent. Samples were collected specifically for this research project.

Sampling method: The principal research question was if hospital inpatients consuming antibiotics were at increased risk of Enterobacteriaceae skin colonization. Therefore participants were assigned to one of two groups (antibiotic group or no antibiotic group) based on their inpatient antibiotic use. The antibiotic group included patients who had consumed > 2 doses of antibiotic whilst an inpatient by the time of sampling. The non antibiotic group, for pragmatic reasons, had consumed ≤ 1 dose of antibiotic at the time of sampling (1 dose = ≥ 1 antibiotic given at one time point). A risk of biasing the antibiotic group to older patients, patients who had been in hospital for longer and patients from certain clinical specialties was identified. To limit this potential bias patients in the antibiotic and no antibiotic groups were matched where possible by duration of hospitalisation (<24 hours, 1-7 days and 8-28 days), clinical speciality (medical and surgical) and by age (+/- 15 years) (See Table II).

Bacterial identification: Swabs were inoculated onto blood and cysteine lactose electrolyte deficient (CLED) agar (E&O, UK), incubated at 37 degrees C for 24 hours. Bacteria were identified using a matrix assisted laser desorption ionisation time of light (MALDI-TOF) mass spectrometry (Bruker, Germany). Antimicrobial susceptibility testing of Enterobacteriaceae was completed according to EUCAST standards. Skin colonization was defined as isolation of ≥ 1 colony of a bacterial species on an agar plate.

Sample size: It was anticipated the rate of Enterobacteriaceae skin colonization was at least 20%. Since the primary analysis was logistic regression, a sample size of 100, giving 20 colonization events, was determined to provide robust estimates for the coefficients of two risk factors allowing the risk of antibiotics to be assessed.³

Statistical analysis: Statistical analyses were performed using Microsoft Open R version 3.2.3. Comparisons of variables of interest between those patients with/without Enterobacteriaceae skin colonization used Pearson's Chi-squared test. Continuous variables were first categorised to aid interpretation and account for nonlinearities. All variables of interest were considered in a logistic regression of Enterobacteriaceae skin colonization. Every combination of eight main effects was considered, giving 256 models. The model with the lowest value of Akaike's Information Criterion (using R package glmulti version 1.0.7) was selected and reported.⁴ The final model was assessed using a Receiver Operating Characteristic (ROC) curve reporting the Area Under the Curve (AUC), sensitivity and specificity which quantify its prediction performance. The ROC curve was generated using the Epi package version 1.1.71.

Results

Patient demographics: In total 100 inpatients were recruited during 2015, see table I. They included sixty patients having received ≤ 1 dose of antibiotic and forty patients having received >2 doses of antibiotic. The characteristics of these groups, including rate of Enterobacteriaceae colonization, with regard to antibiotic use is reported in Table I.

Risk factors for Enterobacteriaceae skin colonization: The Enterobacteriaceae skin colonization rate in patients having received >2 doses of antibiotic was 38% (15/40), higher than the 15% (9/60) in those receiving ≤ 1 dose of antibiotics ($p=0.012$). Univariable analysis identified male sex and inpatient antibiotic use as risk factors for Enterobacteriaceae skin colonization. These were confirmed after multivariable analysis. The adjusted odds ratio for antibiotic use was 3.16 (95% confidence interval, 1.19 to 8.4) and for male sex was 2.92 (1.06 to 8.4). In an assessment of the model, as a result of plotting the ROC curve for the fitted logistic regression, the AUC was determined as 0.71, and the optimum cut point gave sensitivity of 45.8% and specificity of 84.2%. Given the simplicity of the predictor, based only on sex (Male: Yes/No) and antibiotic consumption (Antibiotic consumed: Yes/No) the performance of the model was satisfactory. Only non antibiotic

patients were included in the patients sampled within 24 hours of their hospitalisation, therefore duration of hospitalisation was assessed as a risk factor for Enterobacteriaceae skin colonization. In the exploration of 256 models no significant association between duration of hospitalisation and Enterobacteriaceae skin colonization was noted. Nevertheless the analysis was repeated without those patients who were sampled within 24 hours of their admission to hospital and similar results obtained, although with wider confidence intervals reflecting the lower sample size. The odds ratio for risk of Enterobacteriaceae skin colonization was 3.22 (95% confidence interval 1.06, 9.73) for male sex, and 2.97 (0.98, 9.02) for inpatient antibiotic consumption.

Site of Enterobacteriaceae colonization: Colonization by Enterobacteriaceae was found to mainly occur in the groin, with 13% of patients colonized, 7% were colonized in the axilla, 5% in the nose, 5% on the buttock and 1% on the forearm and hand.

Bacterial species and antibiotic use: The Enterobacteriaceae species identified included three Citrobacter, seven *E.coli*, four Enterobacter, seven Klebsiella, one Morganella, three Pantoea (formally Enterobacter) and four Proteus. The antibiotic susceptibility of these isolates was unrelated to patient's antibiotic use. In total 26 different antibiotic regimens were administered to the 40 patients in the antibiotic group.

Discussion

Hospitalisation has been cited as a risk factor for colonization with Enterobacteriaceae, but evidence supporting this may have been biased by the lack of matching between inpatients and outpatients.^{5/6} Our data suggests that hospitalisation is not a risk factor for skin colonization with Enterobacteriaceae, with patients in hospital for < 24 hours having the same rate of Enterobacteriaceae skin colonisation as those hospitalised for 1-28 days who did not consume antibiotics. Our data suggest that antibiotic consumption and being male are though risk factors for skin colonization with Enterobacteriaceae in hospitalised adults. This data is relatively novel as the

most studies of Enterobacteriaceae colonization have focused almost exclusively on gastrointestinal colonization with resistant Enterobacteriaceae.⁷

Most Enterobacteriaceae skin colonization occurs in the groin and axilla, and it has been suggested before that the groin may act as a permanent source of Enterobacteriaceae skin colonization in some patients.⁸ Both the groin and axilla are rich in sweat glands and this may explain why these sites are most frequently colonized, and why males, with more active sweat glands, are more commonly colonized.⁹ The finding that colonization was higher for patients on antibiotics may relate to the effect of antibiotics on the skin microbiome. Alterations (loss) to the skin microbiome may reduce the resistance to colonization normally provided by commensal bacteria, so called colonization resistance. Interactions between commensal bacteria and the ability of *Staphylococcus aureus* to colonise the nasal cavity have been shown and provide evidence to support the concept of colonization resistance.¹⁰

The study was challenged by being of a pragmatic design being undertaken in a clinical setting. The patients were heterogeneous with regard their underlying conditions and antibiotic regimens. Despite these challenges we identified potential risk factors for Enterobacteriaceae skin colonization with a relatively small number of patients. This small size may have prevented the identification of risk factors which are less strongly associated with Enterobacteriaceae skin colonization. In addition there may have been risk factors which have not been identified and hence not accounted for in the multivariable analysis.

Conclusions

Health care staff should be aware hospitalised male patients and antibiotic treated patients may be at increased risk of Enterobacteriaceae skin colonisation. It may be appropriate in Enterobacteriaceae outbreaks to apply additional infection prevention and control interventions to these patients to reduce Enterobacteriaceae transmission.

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Conflicts on interest: None

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Table I: Demographics and Enterobacteriaceae skin colonization rates for study participants

	All participants	Inpatient Antibiotics	Inpatient No antibiotics	< 24 hours No antibiotics
Number of participants	100	40	40	20
Age: years (mean)	61	61	63	56
Sex: Male	50 (50%)	23 (56%)	16 (40%)	11 (55%)
BMI (mean/range)	29.6	31	29	28
Level of dependence Self caring	84 (84%)	30 (75%)	34 (85%)	20 (50%)
Usual residence Own home	100%	40 (100%)	40 (100%)	20 (100%)
Antibiotics consumed within the 3 months before admission	35 (35%)	20 (50%)	14 (35%)	1 (5%)
Pre-admission chlorhexidine	10 (10%)	1 (3%)	0 (0%)	9 (45%)
Inpatient chlorhexidine	1 (1%)	1 (3%)	0 (0%)	0 (0%)
Enterobacteriaceae skin colonization	24 (24%)	15 (38%)	6 (15%)	3 (15%)

Table II: Stratification and matching of the patients sampled in the Home Guard study, with the total number of patients within each stratification group.

	Length of stay					
	<24 hours		1-7 days		8-28 days	
	Medical patients	Surgical patients	Medical patients	Surgical patients	Medical patients	Surgical patients
Antibiotics	0 ⁵	0 ⁵	10 ¹	10 ²	10 ³	10 ⁴
No antibiotics	10	10	10 ¹	10 ²	10 ³	10 ⁴

1-Matched by age, 2-Matched by age, 3-Matched by age, 4-Matched by age, 5-No patients included as it was not practically possible to sample patients who had > 2 doses of antibiotics within the first 24 hours of their hospital stay.