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Short Report

Duration of carriage of multidrug resistant Enterobacterales in discharged hospital and general practice patients and factors associated with clearance

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SUMMARY

Objectives: Dutch guidelines recommend contact precautions in patients with multidrug resistant microorganisms cultured during the previous 12 months. To evaluate this policy, duration of carriage of multidrug resistant *Enterobacterales* was assessed among discharged hospital patients and patients attending their general practitioner (GP). Additionally, we assessed factors associated with clearance.

Methods: From January 2013 until May 2016, rectal or faecal samples accompanied by questionnaires on patient characteristics were obtained at time of study inclusion and 3, 6 and 12 months later, in 72 patients with multidrug resistant *Enterobacterales*. Clearance was defined as one or more negative cultures without a subsequent positive culture at 12 months after study inclusion. The percentage of clearance, intermittent carriage and persistence was determined and associated factors were assessed by logistic regression analysis.

Results: Clearance was found in 31 patients (43.1% [95%CI: 32.3—54.6]) of which 23 patients had two or more subsequent negative cultures. Twelve patients were classified as intermittent carriers (16.7% [95%CI: 9.8—26.9]) and 29 patients (40.3% [95% CI: 29.7—51.8]) as persistent carriers. Of the intermittent carriers, the majority (n=9) had two negative cultures during the study period. There was no difference in clearance between discharged hospitalized patients and GP patients. The only factor associated with clearance at 12 months in both univariable and multivariable analyses was not traveling to a foreign country (OR=3.5 [95%CI: 1.0—12.4]).

Conclusion: Active screening for clearance of multidrug resistant *Enterobacterales* in patients within the health care setting is probably not beneficial due to high levels of intermittent and persistent carriage.

Abbreviations: GP, general practitioner; HRMO, highly resistant microorganisms; EPD, electronic patient record; ESBL, extended-spectrum beta-lactamase.

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Introduction

To control the transmission of multidrug resistant bacteria, hospitals use infection control measures. In 2004, the Dutch Working Party on Infection Prevention issued a guideline on the prevention of nosocomial transmission of highly resistant microorganisms (HRMO) with criteria for defining HRMO and recommendations on contact precautions, active surveillance, and contact tracing [1]. This guideline, revised in 2013, recommends not to suspend contact precautions in patients with HRMO during hospitalization and to install contact precautions in patients readmitted with HRMO cultured in the previous 12 months [2].

In our hospital, every patient with an HRMO receives an HRMO flag in their electronic patient record (EPD). Conforming with national guideline recommendations, this HRMO flag remains active for one year and is prolonged for an additional year when subsequent cultures also show multidrug resistant bacteria. However, the HRMO flag is removed when two rectal cultures taken on separate days more than48 hours after use of antimicrobial agents, are negative. Both hospitalized patients and patients attending a general practitioner, sending culture specimens to our hospital laboratory, receive an HRMO flag within their EPD if an HRMO is cultured.

To evaluate whether in certain patient groups the HRMO flag can be lifted within 1 year after a positive culture with HRMO, we assessed carriage of multidrug resistant *Enterobacterales* in patients until 12 months after hospital discharge from the Reinier de Graaf Hospital, and among patients attending their general practitioner (GP) in the service area of the Reinier de Graaf Hospital. Additionally, we assessed whether certain patient characteristics, such as co-morbidity, or bacteria characteristics such as species type and the type of resistance, are associated with clearance of multidrug resistant *Enterobacterales*. We thereby hypothesised that a good general health condition reflected by exercise and nutritional status might be important predictors for clearance.

Methods

The Reinier de Graaf Hospital is a 481-bed general teaching hospital in Delft that provides both general and complex care for the 350,000 inhabitants in the service area of the hospital. There is special focus on care for the elderly, oncology and mother- and child care. Resistance levels are in line with other hospitals in the Netherlands with resistance among *Escherichia coli* for extended-spectrum beta-lactamase (ESBL) at 5.6% and combined resistance levels to both fluoroquinolones and aminoglycosides at 7.2% for patients admitted at general hospital departments during the study period [3].

From January 2013 until May 2016, we approached all hospitalized patients with a multidrug resistant *Enterobacterales* cultured during hospitalization for informed consent. Non-hospitalised patients were included by approaching their GP requesting to forward the study information to their patients. Patients were approached irrespective of previous cultures with multidrug resistant *Enterobacterales*. Written informed consent was obtained from all patients. Exclusion criteria were severe morbidity with short life expectancy and patients not mentally able to give informed consent.

Rectal swabs or faecal samples accompanied by questionnaires on patient characteristics (e.g. background data, co-morbidity and information about nutrition and exercises) were obtained at time of study inclusion (T=0) and 3 (T=1), 6 (T=2) and 12 (T=3) months thereafter. We based our questionnaire on previous literature describing risk factors for the acquisition of multidrug resistant *Enterobacterales* [4–7], and additionally included questions on exercise and nutrition based on Dutch guidelines [8,9] to support our hypothesis that general health might be an important predictor for HRMO clearance.

Samples were incubated overnight in a 3ml homemade Tryptone Soya Broth supplemented with vancomycin 8 μg/ml to inhibit growth of Gram-positive micro-organisms. Subsequently the broth was cultured on a Columbia agar with sheep blood supplemented with a disk of Nalidixan 30 μg and Tobramycine 10 μg and on an ESBL agar (Oxoid, Basingstoke, United Kingdom). Phenotypic confirmation of extended-spectrum beta-lactamase (ESBL)-production was performed with cefotaxime, ceftazidime and cefipime disks with and without clavulanic acid (Neo-Sensitabs, Rosco Taastrup, Denmark). MALDI-TOF MS (Bruker Daltonics, Billerica, United States) was used for isolate determination and the Phoenix automated susceptibility testing system to determine antimicrobial susceptibility (Becton Dickenson, Franklin Lakes, United States).

Definitions of the Dutch Working Party on Infection Prevention on HRMO were used, that is phenotypic production of ESBL or a combined resistance to both fluoroquinolones and aminoglycosides [2]. We evaluated the number of patients with one, two or three negative cultures at 12 months and defined clearance of HRMO as one or more negative cultures without a subsequent positive culture at 12 months after study inclusion (that is one or more negative cultures at T=1 and/or T=2 and/or T=3 without subsequent positive cultures) to exclude intermittent carriage. Intermittent carriage was assumed if a patient had a negative culture at T=1 and/or T=2 followed by one or more positive cultures. Patients without negative cultures at T=1, T=2 and T=3 were assumed to be persistent carriers. We calculated the percentage of HRMO clearance, intermittent carriage and persistent carriage, including 95% confidence intervals (95% CI) and determined factors (see Table I) associated with HRMO clearance by univariable and multivariable logistic regression analysis, using backward/forward variable selection including all variables with $p<0.5$ using SPSS statistical software 25.0. Statistical significance was defined as $p<0.05$.

The study was approved by the Medical Ethical Committee of the Reinier de Graaf Hospital.

Results

We included 101 patients, ranging18 to 93 years old (median age 69 years). Table I shows patient and bacteria

Table I
Background, health and bacteria characteristics of the 101 patients included to the study and results of the univariable logistic regression analysis. The background variables were obtained at time of study inclusion; all other variables were obtained 12 months after study inclusion.

Characteristics		n (%)	OR(95%CI)*	P-value
Age (years)	18–54	22 (21.8)[a]		0.2
	55–74	41 (40.6)	0.3 (0.1–1.1)	
	75–93	38 (37.6)	0.8 (0.3–2.2)	
Gender	Female	59 (58.4)[a]	1.4 (0.5–3.8)	0.5
Setting of study inclusion	Hospital	43 (42.6)[a]		0.4
	General practice	58 (57.4)	1.5 (0.6–4.1)	
Domestic animals	No	42 (72.4)[f]	1.9 (0.6–6.5)	0.3
Number of people in the household	>2 persons	86 (85.1)[a]	0.5 (0.1–2.7)	0.4
Underlying morbidity	No	14 (13.9)[a]	0.7 (0.2–2.7)	0.6
Previous culture with multidrug resistant *Enterobacterales*	No	80 (79.2)[a]	0.7 (0.2–2.4)	0.6
Species type	E. coli	85 (84.2)[a]		0.4
	Other species	16 (15,8)[a]	1.7 (0.5–6.3)	
Resistence mechanism	ESBL	69 (68.3)[a]		0.4
	HRMO	32 (31.7)[a]	1.5 (0.5–4.1)	
Culture type	Clinical	78 (74.3)[a]		0.3
	Screening	26 (25.7)[a]	1.9 (0.6–6.2)	
Wounds in the past 3 months	No	55 (87.3)[b]	2.5 (0.5–13.4)	0.3
Urinary catheter in the past 3 months	No	56 (88.9)[b]	1 (0.2–4.9)	1
Urinary tract infection in the past 3 months	No	49 (77.8)[b]	1.6 (0.4–6.1)	0.5
Diarrhoea in the past 3 months	No	53 (84.1)[b]	1.6 (0.5–7.0)	0.5
Antibiotics in the past 3 months	No	44(69.8)[b]	1.7 (0.6–5.5)	0.3
Antacids in the past 3 months	No	30 (47.6)[b]	1.2 (0.4–3.3)	0.7
Hospitalization in the past 3 months	No	54 (85.7)[b]	1.3 (0.3–5.9)	0.8
Attending a foreign country in the past 3 months	No	43 (69.4)[c]	3.5 (1.0–12.4)	0.1
Eating meat	Less than 5 times a week	16 (25.8)[c]	1.3 (0.4–4.3)	0.7
	More than 5 times a week	46 (74.2)		
Eating fruit	At least 2 times a day	26 (41.9)[c]	0.9 (0.3–2.5)	0.8
Eating vegetables	At least 200 grams a day	8 (13.1)[d]	2.0 (0.6–6.9)	0.3
Eating Fish	2 times a week	11 (18.0)[d]	0.7 (0.2–2.8)	0.7
Physical activity	30 min/day at least 5 times a week	32 (53.3)[e]	1.4 (0.5–4.0)	0.5

* Univariable logistic regression analysis of multidrug resistant *Enterobacterales* clearance versus intermittent and persistent carriage based on the 72 patients that completed follow-up.
[a] N=101.
[b] N=63.
[c] N=62.
[d] N=61.
[e] N=60.
[f] N=58. Variations in number of patients are due to incomplete questionnaires 12 months after study inclusion.

characteristics at study inclusion and the patient health characteristics 12 months after study inclusion. Over 40% of the patients were included from the hospital setting, most had underlying morbidity (86.1%) and 20.8% of patients already had an HRMO cultured before study inclusion. HRMO were mostly identified from clinical cultures, only 25.7% were cultured from screening cultures. *Escherichia coli* was the most frequent HRMO at inclusion (84.2%), and the most common resistance mechanism was phenotypically ESBL production (68.3%). Other *Enterobacterales* found were *Klebsiella pneumoniae* (9%) and *Proteus mirabilis* (5%).

In total, 74 patients completed follow-up. Loss to follow-up was due to unexpected terminal morbidity (n=2), dementia (n=1), mortality (n=12), long-term antimicrobial use (n=1) or withdrawal from the study (n=11). Two additional patients were excluded due to missing culture results at T=1, leaving a total of 72 patients for analysis. Of these 72 patients, 19 patients (26.4%) were culture negative for HRMO at 3, 6 and 12 months, 4 patients (5.5%) were cultured negative at 6 and 12 months and 13 patients (18.1%) had a negative culture at 12 months of which 5 also had a negative culture at 3 months.

HRMO clearance at 12 months after study inclusion (T=3) was found in 31 patients (43.1% [95%CI: 32.3–54.6]) of which 23 patients had two or more subsequent negative cultures. Twelve patients were classified as intermittent carriers (16.7% [95%CI: 9.8–26.9]) and 29 patients (40.3% [95% CI: 29.7–51.8]) as persistent carriers (Figure 1). There was no difference in HRMO clearance between discharged hospitalized patients and GP patients. Figure 1 shows the absolute number of patients with multidrug resistant *Enterobacterales* clearance, and intermittent and persistent carriage over time. Nineteen patients (26.4%) had three negative cultures during the study period and

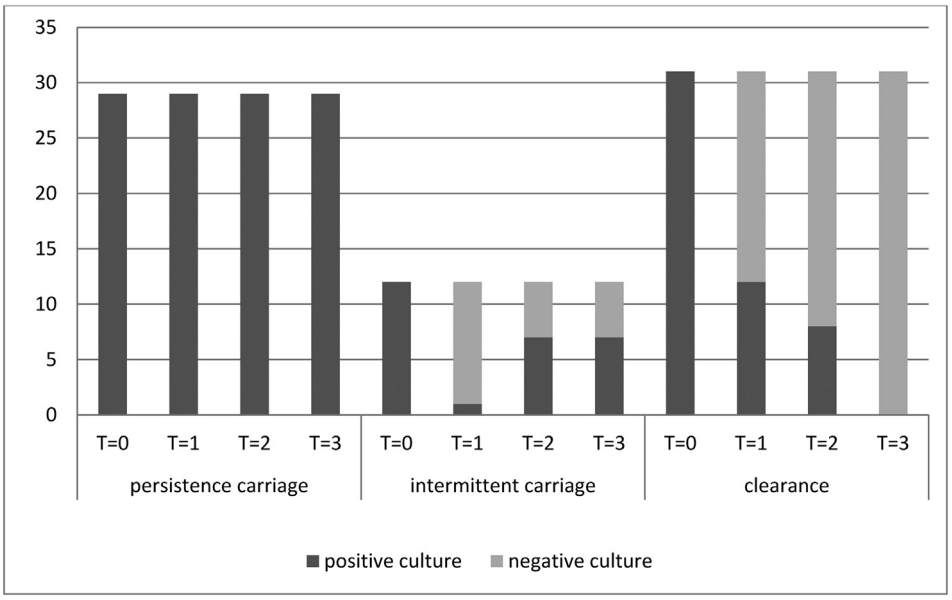

Figure 1. Absolute number of patients with multidrug resistant *Enterobacterales* persistent and intermittent carriage and clearance over time at 3 (T=1), 6 (T=2) and 12 months (T=3) after study inclusion (T=0). Clearance was defined as one or more negative cultures at T=1 and/or T=2 and/or T=3 without subsequent positive cultures. Of the intermittent carriers 5 were negative at T=1 and T=3 and positive at T=2; 4 were negative at T=1 and T=2 and positive at T=3; 2 were negative at T=1 and positive at T=2 and T=3; 1 was positive at T=1 and T=3 and negative at T=2.

were considered as HRMO cleared within 6 months after inclusion. Of the intermittent carriers, the majority (n=9) had two negative cultures during the study period of which four patients had two subsequent negative cultures at T=1 and T=2. All cultures demonstrated identical species over time among persistent and intermittent carriers. The only factor showing a borderline significant trend with HRMO clearance at T=3 in both univariable and multivariable analyses was not traveling to a foreign country in the past three months (OR=3.5 [95%CI: 1.0—12.4], Table I).

Discussion

In our setting, approximately one-fourth of patients had multiple negative cultures for HRMO 6 months after study inclusion, thereby qualifying for early removal of the HRMO flag within their EPD. However, we did not identify patient characteristics predicting HRMO clearance. The only association found was the higher risk of persistent and intermittent carriage related to travel which might be explained by a higher risk of acquisition of multidrug resistant bacteria abroad as reported in other studies [10,11].

In our study, the percentage of intermittent and persistent carriers was relatively high (57%), while other studies reported persistence rates around 30 to 40% after 12 months [12,13]. A possible explanation for the higher persistence rate might be due to differences in the definition of persistence and clearance. The systematic review by Bar-Yoseph *et al*, showed that the rates for clearance are higher when only a single sample defines clearance versus multiple samples [12]. In our study, clearance was defined as one or more negative cultures without a subsequent positive culture at 12 months after study inclusion. Additionally, another explanation might be the high prevalence of underlying morbidity in our population (86% of the participants had underlying morbidity). Morbidity might lead to more hospital admissions and/or antimicrobial usage which are risk factors for HRMO colonization [5—7]. Finally, the laboratory method used might influence the yield of HRMO cultures. We used broth enrichment since the Dutch guideline for the detection of HRMO suggested higher yield with broth enrichment, although without enough evidence supporting a positive recommendation, when compared to traditionally selective agars [14,15]. Since the guideline publication in 2012, studies have demonstrated a significant and relevant more yield when using pre-enrichment [16,17].

Our study is limited by the relative few sampling times, the loss to follow-up and recall bias by retrospective questionnaires. However, most of the loss to follow-up was explained by the health status of participants. The questionnaires were mainly on exercise and nutritional habits which are not likely to vary largely over time.

We established rates of clearance and intermittent and persistent carriage of HRMO in a representative cohort of Dutch discharged hospital and GP patients and evaluated factors such as nutritional and health-wellbeing status, to our knowledge not earlier studied, on HRMO clearance. We also showed that HRMO clearance might already be identified early after discharge since most of these patients were negative (and remained negative) within 6 months after inclusion. However, the 19 patients showing early HRMO clearance were only the minority of the 72 patients followed and none of the factors studied were helpful in predicting which patients might qualify for early removal of the HRMO flag within the EPD. Additionally, eight patients considered HRMO cleared were based on only one negative culture at T=3 (Figure 1). Given the substantial part of patients that were intermittent carriers, among which several had two negative cultures, one culture defining HRMO clearance is clearly not sufficient. Multiple (two or even more)

negative rectal or faeces cultures, using sensitive laboratory protocols, are necessary before an HRMO flag can be removed from the EPD, while a selective active screening strategy based on patient characteristics is unfortunately unavailable. Due to the high levels of intermittent and persistent carriage found in our study it seems unlikely that active screening for HRMO clearance in the health care setting will lead to an early removal of HRMO flags in a substantial part of patients, while risking intermittent carriage and admitting these patients without contact precautions.

Conclusion

Although, unnecessary installation of contact precautions puts pressure on single room capacity within hospitals and is time-consuming for health professionals it seems that active screening for clearance of multidrug resistant *Enterobacterales* in patients within the health care setting is probably not beneficial due to high levels of intermittent and persistent carriage.

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Contribution

Study design: AB, EV, LN, SE
Data collection: AB, EV, LN, SE
Statistical analysis and interpretation: CW, AB
Drafting of manuscript: CW, AB
Revising the manuscript critically for important intellectual content: EV, LN, SE
All authors have seen and approved the final article.

Conflict of interest statement

None declared.

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