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ORIGINAL RESEARCH

Modelling and Simulation of the Effect of Targeted Decolonisation on Incidence of Extended-Spectrum Beta-Lactamase-Producing *Enterobacterales* Bloodstream Infections in Haematological Patients

Stefanie Döbele · Fulvia Mazzaferri · Tamara Dichter · Gerolf de Boer · Alex Friedrich · Evelina Tacconelli

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ABSTRACT

Introduction: Haematological patients are at higher risk of bloodstream infections (BSI) after chemotherapy. The aim of this study was to develop a simulation model assessing the impact of selective digestive decontamination (SDD) of haematological patients colonised with extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E) on the incidence of ESBL-E BSI after chemotherapy.

Methods: A patient population was created by a stochastic simulation model mimicking the patients' states of colonisation with ESBL-E during hospitalisation. A systematic literature search was performed to inform the model. All ESBL-E carriers were randomised (1:1) to either the intervention (targeted SDD) or the control group (placebo). ESBL-E BSI incidence was the outcome of the model. Sensitivity analyses were performed by prevalence of ESBL-E carriage at hospital admission (low: < 10%, medium: 10–25%, high: > 25%), duration of neutropenia after receiving chemotherapy, administration of antibiotic prophylaxis with quinolones, and time interval between SDD and chemotherapy.

Results: The model estimated that the administration of targeted SDD before chemotherapy reduces the incidence of ESBL-E BSI in the hospitalised haematological population up to 27%. The greatest benefit was estimated in high-prevalence settings, regardless of the duration of neutropenia, the time interval before chemotherapy, and the administration of antibiotic prophylaxis with quinolones ($p < 0.05$). In medium-prevalence settings, SDD was effective in patients receiving quinolone prophylaxis, with either 1-day time interval before chemotherapy and a neutropenia duration > 6 days ($p < 0.05$) or 7-day time interval before chemotherapy and a neutropenia duration > 9 days ($p < 0.05$). No benefit was observed in low-prevalence settings.

Conclusions: Our model suggests that targeted SDD could decrease the rate of ESBL-E BSI in haematological carriers before chemotherapy in

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the setting of high ESBL-E prevalence at hospital admission. These estimates require confirmation by well-designed multicentre RCTs, including the assessment of the impact on resistance/disruption patterns of gut microbiome.

Keywords: Bloodstream infection; Decolonisation; *Enterobacterales*; Extended spectrum beta lactamases (ESBLs); Haematological malignancies; Infection control; Modelling; Neutropenia

Key Summary Points

Why carry out this study?

Haematological patients are at higher risk of bloodstream infections after undergoing chemotherapy.

The aim of this study was to develop a simulation model assessing the impact of selective digestive decontamination (SDD) of haematological patients colonised with extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E) on the incidence of ESBL-E BSI after chemotherapy.

The model estimations will drive future studies to assess the effect of targeted SDD on clinical, microbiological, and epidemiological outcomes, including the impact on resistance to antibiotics.

What was learned from the study?

The model estimated a reduction in the incidence of ESBL-E BSI after chemotherapy in the targeted SDD group: the greatest benefit was estimated in high-prevalence settings at hospital admission, regardless of the duration of neutropenia, the time interval before chemotherapy, and the administration of antibiotic prophylaxis with quinolones.

Our model suggests that targeted SDD could decrease the rate of ESBL-E BSI in haematological carriers before chemotherapy in the setting of high ESBL-E prevalence at hospital admission.

These estimates require confirmation by well-designed multicentre RCTs, including the assessment of the impact on resistance/disruption patterns of gut microbiome.

INTRODUCTION

Neutropenia is the most frequent host-cell defect in patients affected by haematological malignancies and increases the risk of development of severe infections, such as bacterial and fungal sepsis [1, 2]. Recommendations from international guidelines suggest antibiotic prophylaxis in patients with high risk of prolonged neutropenia after chemotherapy [3, 4]. An updated systematic review with meta-analysis of fluoroquinolone-based antibacterial chemoprophylaxis in neutropenic patients with haematological malignancies from the European Conference on Infections in Leukaemia (ECIL) reported fewer febrile episodes (pooled odds ratio [OR] 0.32, 95% CI 0.20–0.50) and fewer bloodstream infections (OR 0.57, 95% CI 0.43–0.74) but no effect upon all-cause mortality (pooled OR 1.01, 95% CI 0.73–1.41) [5–7]. However, the effectiveness of prophylaxis is now under discussion because of the change in the epidemiological scenario of bloodstream infections (BSI) and the risk of promoting resistance among both gram-negative and gram-positive bacteria [8–19].

Due to an empty pipeline, infection control measures could play a pivotal role in controlling the spreading of ESBL-E in health-care settings [20]. Among them, decolonisation strategies, defined as any measure that leads to loss of ESBL-E detectable carriage and validated mainly in the intensive care unit (ICU) setting, seem promising [21–26]. The first assumption underlying decolonisation strategies is that

colonisation increases the risk for subsequent infections [27].

To date, the role of SDD targeting ESBL-E has not been investigated in haematological neutropenic patients. We developed a stochastic simulation model to assess the impact of targeted SDD (decolonisation of ESBL-E carriers) on the incidence of ESBL-E BSI in patients with haematological malignancies after the first cycle of chemotherapy, according to the prevalence of ESBL-E carriage at hospital admission, the administration of antibiotic prophylaxis with quinolones, the time interval between SDD and chemotherapy, and the duration of neutropenia. The model estimations will drive future studies to assess the effect of targeted SDD on clinical, microbiological, and epidemiological outcomes, including the impact on resistance to antibiotics.

METHODS

Baseline Model

We developed a stochastic simulation model which created a population of patients with haematological malignancies who were admitted to the haematological ward for the first cycle of chemotherapy, mimicking the patients' states of colonisation and/or infection with ESBL-E during hospitalisation (Markov chain Monte Carlo simulation model) [28]. After admission, all ESBL-E carriers were randomised (1:1) to either the intervention (targeted SDD) or the control group (placebo). ESBL-E BSI incidence was the outcome in this model. To increase the internal validity, a second analysis of universal SDD (not targeting ESBL-E carriers) was performed (see Tables S1–S2–S3 in the electronic Supplementary Material).

Sensitivity analyses were performed to assess the impact of different parameters on the efficacy of SDD. The assessed parameters were the prevalence of ESBL-E carriage at hospital admission, the duration of neutropenia after receiving chemotherapy, the administration of antibiotic prophylaxis with quinolones, and the time interval between SDD and chemotherapy.

The model was developed and informed using both published evidence and unpublished data (local data recorded at the hematological department of the University of Groningen and unpublished data from the European-funded SATURN project [29]). A systematic literature search was performed to inform the model on the effect of decolonisation on carriers of ESBL-E. Articles were identified through computerised literature searches using PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Web of Science and by reviewing the references of retrieved articles. Index search terms included: (Citrobacter OR Enterobacter OR Escherichia OR Klebsiella OR Morganella OR Proteus OR Providencia OR Serratia OR Enterobacteriaceae OR Enterobacterales OR coliform OR gram-negative bacteria) AND (cephalosporin-resistan* OR cephalosporin resistan* OR beta-lactamase OR beta lactamase) AND (decolon* OR decontamin* OR eradicat* OR suppress*). The search was restricted to full articles published in English up to 2019 including adult hospitalised patients (> 16 years of age). Articles reporting interventions in specific hospital settings not involving haematological patients (i.e. ICU, solid organ transplantation) were excluded.

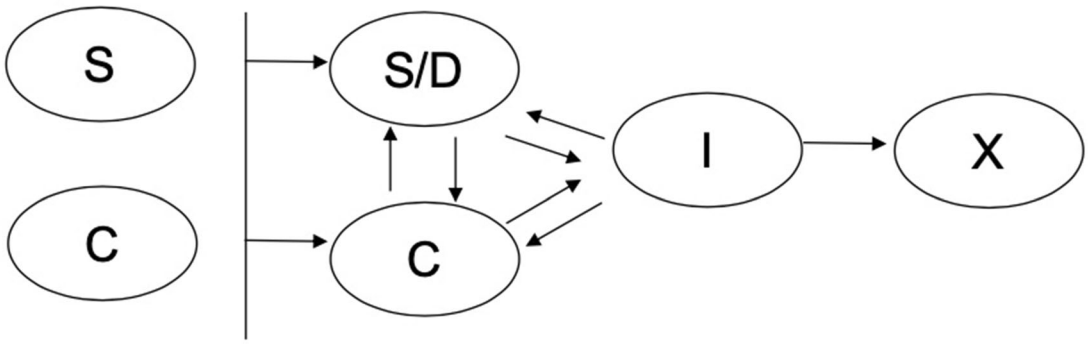
Patients could display five different states related to ESBL-E: susceptibility to colonisation (S); colonisation (C); ESBL-E BSI (I); decolonisation after SDD, ESBL-E BSI treatment, or spontaneously (D); death after ESBL-E BSI (X). Figure 1 shows the model pathways.

The model input parameters are reported in a dedicated section of the results and in Table 1.

As this article is based on previously conducted studies, it does not contain any new studies with human participants or animals performed by any of the authors.

Statistics and Modelling

A Markov chain Monte Carlo simulation was performed. The simulation model drew the number of patients in the ward, the absolute neutrophil count, and the patients' state related to ESBL-E. Daily probabilities of state transitions were assigned by taking the 30th fractional matrix root of the 30-day probabilities (or analogue the 7th/28th fractional matrix root of the



S, not colonised and susceptible for colonisation; C, colonised with ESBL-E but not infected with ESBL-E; I, affected by ESBL-E BSI; D, decolonised (after SDD or ESBL-E BSI treatment or spontaneously); X, death after ESBL-BSI.

Fig. 1 States of patients with haematological malignancies with regard to colonisation and infection due to ESBL-E

7/28 day-probabilities). Results were adapted using a stochastic matrix. Considering that the state transition model consisted of more than two states, a differential evolution algorithm was applied for optimisation [30]. State transition probabilities were adjusted dynamically, where necessary. The cohort models were applied to 75,000 patients per run (two runs: targeted SDD and universal SDD). Simulation data were summarized in pivot tables (see Table 2 and Table S1 in the electronic Supplementary Material). All the values of the variables were reported in a summary file per run. The overall results were combined automatically by the summary module. Two-sided p values < 0.05 were considered significant (Mann-Whitney-Wilcoxon test). p values were determined in cross-run comparisons to assess differences in ESBL-E BSI rates between different values of parameters (i.e. low vs. medium prevalence of ESBL-E carriage at hospital admission).

RESULTS

Model Input Parameters

The systematic literature search identified one RCT [31] and one prospective cohort study [32] assessing the effectiveness of SDD on ESBL-E rectal carriage in adult hospitalised patients. Huttner et al. allocated 54 patients to either placebo or oral colistin sulphate (50 mg four times daily) and neomycin sulphate (250 mg four times daily) for 10 days (plus nitrofurantoin for 5 days in case of urine detection). A significantly lower rectal carriage was observed in the treatment group at the end of treatment, 32% (8/25) vs. 76.9% (20/26; $p = 0.001$). The effect turned out to be not significant at 7-day [66.7% (18/27) vs. 68% (17/25), $p = 0.92$] and at 28-day post-treatment [51.9% (14/27) vs. 37% (10/27), $p = 0.28$] [31]. In an 8-year prospective cohort study, Buehlmann et al. enrolled 35 asymptomatic ESBL-E carriers and treated with chlorhexidine mouth rinse for 4 days for throat colonisation, oral paromomycin for 4 days for rectal colonisation, or oral nitrofurantoin or fosfomycin (single dose) or ciprofloxacin or cotrimoxazole for 5 days for urinary colonisation. The course was repeated in patients with persistent ESBL-E carriage, showing that repeated decolonisation significantly improved eradication rate at treatment end [88.9% (16/18) vs. 41.1% (7/17); $p = 0.007$] [32]. No clinical outcomes were analysed in either of the two studies [31, 32]. On the basis of the higher level of evidence displayed by the RCT [31], the modelled SDD regimen consisted of oral colistin sulphate (50 mg four times daily) and neomycin sulphate (250 mg four times daily) for 10 days.

Table 1 State transition probabilities according to data retrieved from literature

State	Probability, %	Time frame, days	Author (year of publication)
I → X	30	30	Kang (2012) [67], Liss (2012) [49]
C → I	9	30	Vehreschild (2014) [34], Liss (2012) [49], Arnan (2011) [35], Reddy (2007) [68]
S → I	0.23	30	Vehreschild (2014) [34], Liss (2012) [49], Arnan (2011) [35], Reddy (2007) [68]
S → C (with antibiotic therapy)	28	30	De Angelis G (2012) [29], Tacconelli (2020) [50]
S → C (without antibiotic therapy)	6.8	30	De Angelis G (2012) [29], Tacconelli (2020) [50]
S → C (cross-transmission)	0.17	30	Fankhauser (2009) [69],Tschudin-Sutter (2012) [70], Hilty (2012) [71]
C → S (spontaneous decolonisation)	37	28	Huttner (2013) [31], Vehreschild (2014) [34], De Angelis G (2012) [29]
I → C	15	30	De Angelis G (2012) [29]
I → S	55	30	De Angelis G (2012) [29], Buehlmann (2011) [32]
C → D	68	1	Huttner (2013) [31]
	33	7	Huttner (2013) [31]
	52	28	Huttner (2013) [31]

S, not colonised and susceptible for colonisation; C, colonised with ESBL-E but not infected with ESBL-E; I, ESBL-E BSI; D, decolonised (after SDD or ESBL-E BSI treatment or spontaneously); X, death after ESBL-E BSI

The modelled population consisted of patients with haematological malignancies who were admitted to a 37-bed haematological department at a tertiary care hospital for the first cycle of chemotherapy with a normal absolute neutrophil count and with a probability of being ESBL-E carriers given by the prevalence of ESBL-E at hospital admission (low: < 10%, medium: 10–25%, high: > 25%) [33]. The length of hospital stay was assumed to be 30 days [34, 35]. The SDD regimen, colistin sulphate (50 mg four times daily) and neomycin sulphate (250 mg four times daily) for 10 days, was administered at 1, 7, or 28 days before chemotherapy over 10 days [31]. After chemotherapy, patients were expected to develop neutropenia (< 500/µl), lasting 3, 6, 9, 12, or 15 days [3, 36]. It was simulated that 50% of the admitted population received fluoroquinolones as antibiotic prophylaxis [37].

Table 1 shows the estimated transition rates from one state to another during hospitalisation, based on data retrieved from the systematic literature search. During hospitalisation the daily rate of transition from one state to another was assumed constant [38]. The ESBL-E acquisition rate among susceptible patients was modelled taking into account patient-to-patient transmission (directly or through contaminated hands of healthcare workers) and environmental reservoirs [39]. The ESBL-E acquisition rate was assumed constant from environmental reservoirs and proportional to the colonisation rate in the ward considering patient-to-patient-

Table 2 Statistically significant differences (p value < 0.05) in ESBL-E BSI incidence between the targeted SDD arm and the control group in the single parameter analysis (pivot table)

Time interval between SDD and chemotherapy (days)	ESBL-E prevalence	Duration of neutropenia (days)	Prophylaxis with quinolones	p value
1	0,18	6	Yes	0,0129
1	0.18	9	Yes	0.0247
7	0.18	9	Yes	0.0486
1	0.18	12	Yes	0.0457
1	0.18	15	Yes	0.0497
7	0.18	15	Yes	0.0372
7	0.29	3	No	0.0346
1	0.29	6	No	0.0143
7	0.29	6	No	0.0079
28	0.29	6	No	0.0269
1	0.29	9	No	0.0127
7	0.29	9	No	0.0124
28	0.29	9	No	0.0088
1	0.29	12	No	0.0037
7	0.29	12	No	0.0103
28	0.29	12	No	0.0090
1	0.29	15	No	0.0298
7	0.29	15	No	0.0215
1	0.29	3	Yes	0.0234
7	0.29	3	Yes	0.0420
28	0.29	3	Yes	0.0348
1	0.29	6	Yes	0.0164
7	0.29	6	Yes	0.0030
28	0.29	6	Yes	0.0155
1	0.29	9	Yes	0.0200
7	0.29	9	Yes	0.0091
28	0.29	9	Yes	0.0006
1	0.29	12	Yes	0.0070
7	0.29	12	Yes	0.0016
28	0.29	12	Yes	0.0082
1	0.29	15	Yes	0.0008

Table 2 continued

Time interval between SDD and chemotherapy (days)	ESBL-E prevalence	Duration of neutropenia (days)	Prophylaxis with quinolones	*p* value
7	0.29	15	Yes	0.0024
28	0.29	15	Yes	0.0087

BSI bloodstream infection, *ESBL-E* extended-spectrum beta-lactamase-producing *Enterobacterales*, *SDD* selective digestive decontamination

transmission [38]. The model included a constant rate of spontaneous ESBL-E decolonisation.

Model Simulations

The effect of SDD on ESBL-E BSI incidence rate had the greatest benefit in the setting of high prevalence at hospital admission. In this setting, targeted SDD significantly reduced the ESBL-E BSI incidence rate, regardless of the duration of neutropenia ($p < 0.05$) (see Tables 2, 3, 4), the SDD time interval before chemotherapy ($p < 0.03$) (see Tables 2, 5, 6), and the administration of antibiotic prophylaxis ($p < 0.05$) (see Table 2 and Fig. 2a, b).

In medium-prevalence settings, the difference in the ESBL-E BSI incidence rate between the targeted-SDD group and the control group turned out to be significant in patients receiving quinolone prophylaxis, with either 1-day SDD time interval before chemotherapy and a duration of neutropenia > 6 days ($p < 0.05$) or 7-day SDD time interval and a duration of neutropenia > 9 days ($p < 0.05$) (see Table 2). In low-prevalence settings, the difference between the two groups was not statistically significant, regardless of the time of SDD administration, administration of prophylaxis, or the duration of neutropenia (see Table 2).

DISCUSSION

This simulation model in a haematological population suggests that the benefit of the targeted SDD administration before chemotherapy varies largely, according to the prevalence of ESBL-E carriage at hospital admission, the duration of neutropenia after receiving chemotherapy, the administration of antibiotic prophylaxis with quinolones, and the time interval between SDD and chemotherapy. The most significant effect was observed in high-prevalence settings, when SDD was provided 1 day before the beginning of chemotherapy in high-risk patients expecting prolonged neutropenia.

Table 3 Percentage fraction of ESBL-E BSI incidence in targeted SDD arm over control arm depending on neutropenia duration (columns) and ESBL-E prevalence at hospital admission (rows)

ESBL-E prevalence	Neutropenia duration (days)					
	3 (%)	6 (%)	9 (%)	12 (%)	15 (%)	Total (%)
0.07	90.15	90.78	88.32	90.35	90.73	90.07
0.18	82.70	81.48	81.10	80.49	82.13	81.57
0.29	77.02	75.15	72.26	73.31	75.27	74.56

BSI bloodstream infection, *ESBL-E* extended-spectrum beta-lactamase-producing *Enterobacterales*, *SDD* selective digestive decontamination

Table 4 Efficacy of targeted SDD *vs.* placebo in reducing ESBL-E BSI incidence depending on neutropenia duration (columns) and ESBL-E prevalence at hospital admission (rows)

p values (mean)	Neutropenia duration (days)					
ESBL-E prevalence	**3**	**6**	**9**	**12**	**15**	**Total**
0.07	0.494	0.512	0.398	0.462	0.471	0.468
0.18	0.165	0.126	0.107	0.090	0.119	0.121
0.29	0.040	0.022	0.007	0.009	0.018	0.019

BSI bloodstream infection, *ESBL-E* extended-spectrum beta-lactamase-producing *Enterobacterales*, *SDD* selective digestive decontamination

Table 5 Percentage fraction of ESBL-E BSI incidence in targeted SDD arm over control arm depending on the time interval between SDD and chemotherapy (columns) and the ESBL-E prevalence at hospital admission (rows)

ESBL-E prevalence	Time interval between SDD and chemotherapy (days)			
	1 (%)	**7 (%)**	**28 (%)**	**Total (%)**
0.07	89.38	88.85	92.03	90.07
0.18	82.92	81.44	80.37	81.57
0.29	74.67	74.68	74.32	74.56

BSI bloodstream infection, *ESBL-E* extended-spectrum beta-lactamase-producing *Enterobacterales*, *SDD* selective digestive decontamination

Table 6 Efficacy of targeted SDD vs. placebo in reducing ESBL-E BSI incidence depending on the time interval between SDD and chemotherapy (columns) and the ESBL-E prevalence at hospital admission (rows)

p values (mean)	Time interval between SDD and chemotherapy (days)			
ESBL-E prevalence	**1**	**7**	**28**	**Total**
0.07	0.433	0.388	0.582	0.468
0.18	0.148	0.114	0.102	0.130
0.29	0.023	0.021	0.014	0.019

BSI bloodstream infection, *ESBL-E* extended-spectrum beta-lactamase-producing *Enterobacterales*, *SDD* selective digestive decontamination

The results of this simulation model are consistent with the observation that ESBL-E colonisation increases the risk of ESBL-E BSI [13, 34]. A systematic review of the link between colonisation and subsequent ESBL-E infection in patients with solid or haematological malignancies, including 10 observational studies and 2211 patients, showed a 13-fold increase in infection risk associated with colonisation [13]. The rates of ESBL-E colonisation in haematological patients display a huge variability between different countries and

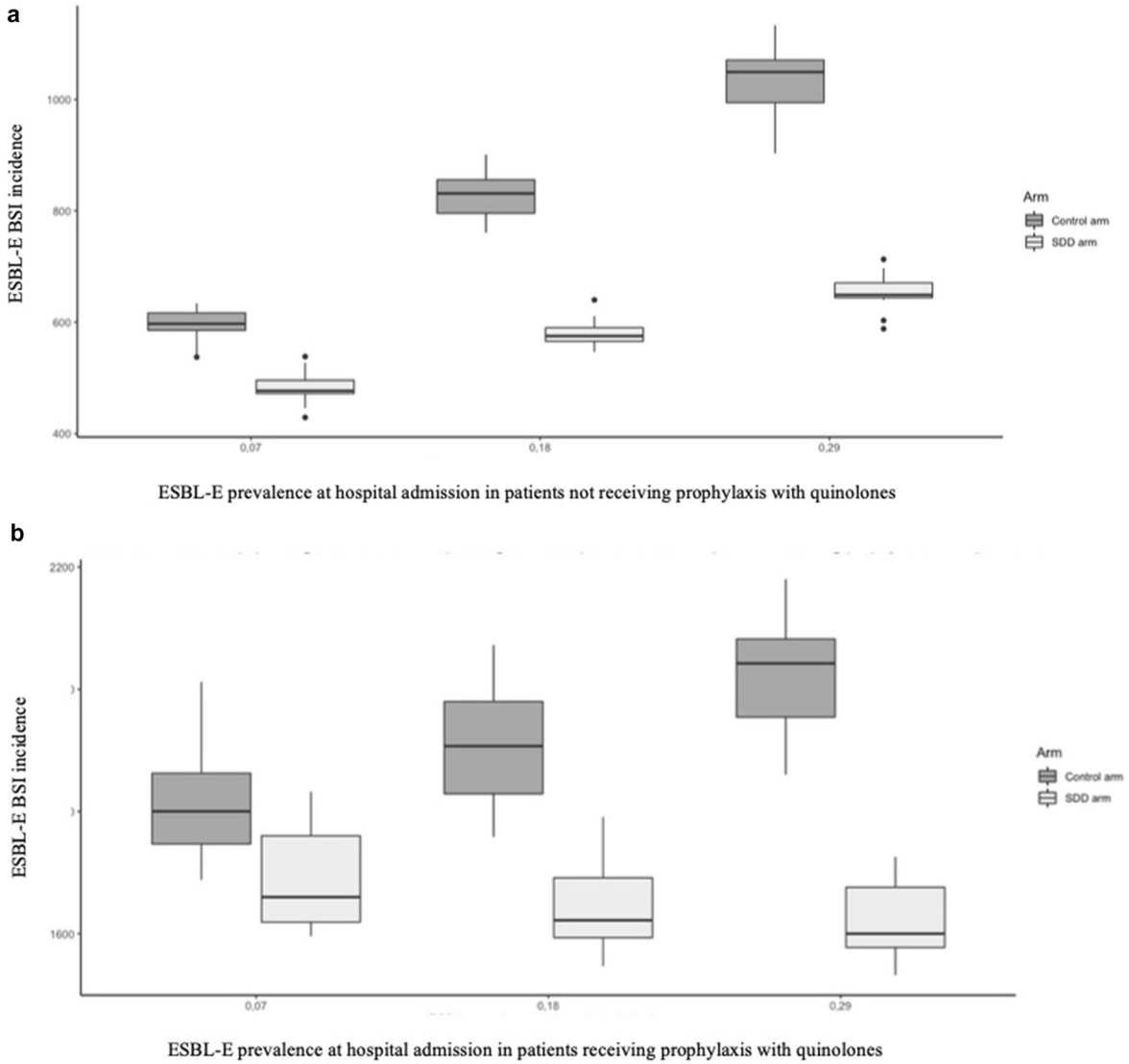


Fig. 2 **a** ESBL-E BSI incidence, depending on the ESBL-E prevalence at hospital admission, in patients not receiving prophylaxis with quinolones. The grey plots show patients in the control arm. The white box plots show patients in the targeted SDD arm. **b** ESBL-E BSI incidence, depending on the ESBL-E prevalence at hospital admission, in patients receiving prophylaxis with quinolones. The grey plots show patients in the control arm. The white box plots show patients in the targeted SDD arm

geographic areas, ranging from 13% in Western Europe to 57% in Southeast Asia, and even between different hospitals within the same country or region [13]. A German prospective observational study in 497 haematological patients showed an ESBL-prevalence at hospital admission of 11% (mainly *Escherichia coli*), ranging from 6 to 23%, and identified previous colonisation with extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E) as the most important risk factor for ESBL-E bloodstream infections (BSIs) [34].

Colonised patients enhance also the likelihood of horizontal transmission. Although the burden has not been specifically estimated in the haematological ward, active surveillance screening of multidrug-resistant strains and strict adherence to contact precautions in case

of colonization or infection should be applied to prevent the further spread of these resistant pathogens in case of endemicity or outbreaks [36].

Longer duration of neutropenia has also been associated with an increased risk of BSI and other infections due to resistant pathogens [36, 40]. Current guidelines recommend antibiotic prophylaxis with quinolones in haematological high-risk patients with prolonged (> 7 days) or profound (absolute neutrophil count < 100/μl) neutropenia [3]. Literature displays limited evidence on the emergence of ESBL-producers associated with antibiotic prophylaxis with quinolones and retrieved results are contradictory. In institutions and geographic regions in which there are high rates of fluoroquinolone resistance, the use of these agents for prophylaxis is less likely to be effective [41, 42]. While most studies showed no significant impact on resistance rates, others reported an increase in infections caused by ESBL-E [5, 8–11]. In particular, quinolones have shown to reduce the rate of susceptible intestinal pathogens and promote the selection and growth of ESBL-E strains [43, 44]. In one prospective study, haematopoietic cell transplant recipients who were colonized with levofloxacin-resistant extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E) pre-transplant and received levofloxacin prophylaxis showed high rates of bacteraemia from their colonizing strains during neutropenia [45]. Interestingly, previous studies identified the prior use of quinolones as a significant risk factor associated with ESBL-E bacteraemia in cancer patients [46–49]. A recent multicentre prospective cohort study, assessing the impact of antibiotics on resistance selection at intestinal level, showed that the administration of monotherapy with quinolones ranked high in promoting ESBL-E colonisation [50]. This evidence is consistent with our results and could explain the greater benefit of targeted SDD on ESBL-E BSI incidence in both patients with prolonged neutropenia and haematological patients receiving antibiotic prophylaxis.

The most extensive experience in universal decolonisation (decolonisation of all patients without previous screening) is with oral non-absorbable selective digestive decontamination (SDD) in ICU patients. Randomised controlled trials (RCTs) performed in low and high endemicity settings of multidrug-resistant gram-negative bacteria showed that universal SDD was effective in reducing infections caused by multidrug-resistant gram-negative bacteria in both settings, with limited impact on selection for new resistance [22–25, 51, 52]. Only one randomized controlled trial assessed the effect of a targeted SDD regimen on ESBL-E carriage in a mixed hospital population, demonstrating a temporary reduction in the carriage rate [31]. Resistance induction or selection represents the major potential drawback of decolonisation. While some studies reported an increased development of resistance to decolonisation therapy, particularly pointing out the appearance of resistance in gram-negative bacteria after the administration of colistin [53–56], others showed no significant increase in antibiotic resistance [22, 51, 57–61]. In theory, SDD might increase the risk on selecting pan-resistant strains. On the other hand, high intraluminal levels of antibiotics exceed minimum inhibition concentrations of resistant pathogens, leading at least to temporary suppression, which reduces the risk of overgrowth and cross-transmission. Further studies with detailed microbiological surveillance are needed to determine the ecological safety of SDD.

This study is subject to limitations, mainly due to the limited available evidence on which model parameter values were based. A few, non-comparative studies, targeting carbapenem-resistant *Enterobacterales* only, evaluated the efficacy of SDD in the haematological setting [62–66]. The investigated SDD regimen relies on the only high-quality RCT assessing the effect of SDD on ESBL-E carriage, which was conducted in a mixed hospital population [31]. An ideal model would be constructed from a prospective registry of neutropenic patients treated with chemotherapy, in which data on a variety of clinical and epidemiological measures could be collected. The SDD duration was not investigated in this study, assuming a 10-day course of oral colistin and neomycin [31]. Nevertheless, based on the evidence for the temporary effectiveness of decolonisation on ESBL-E rectal

carriage [31], it would be reasonable to start the SDD shortly before the neutropenia-inducing chemotherapy and to extend the administration until the resolution of neutropenia. Due to the lack of specific data, the model could not explore the SDD effect on either the selection of strains resistant to decolonising agents or microbiome disruption. For the same reason, only the first cycle of chemotherapy was considered, even though a possible subsequent development of resistance could minimise the SDD benefit in the following cycles.

CONCLUSIONS

Considering that rates of colonisation and infection with ESBL-E vary considerably between study sites, our data may support SDD in high-incidence settings, whereas the cost-benefit ratio may not be satisfactory in medium- or low-incidence settings. These estimates require confirmation by well-designed multicentre RCTs in the setting of high ESBL-E prevalence at hospital admission, administering targeted SDD shortly before the neutropenia-inducing chemotherapy. Future studies should be conducted to determine the effect of decolonisation strategies on clinical, microbiological, and epidemiological outcomes, including the assessment of the impact on resistance/disruption patterns of gut microbiome.

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Disclosures. Stefanie Döbele, Fulvia Mazzaferri, Tamara Dichter, Gerolf de Boer, Alex Friedrich, and Evelina Tacconelli have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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