

# High Acquisition Rate of Gram-Negative Multi-Drug Resistant Organism Colonization During Hospitalization: A Perspective from a High Endemic Setting

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**Objective:** The aim of the study was to compare the rate of gram-negative multi-drug resistant organism (GN-MDRO) colonization at admission and during hospitalization and to describe the strains and antibiotic resistance genes acquired during hospitalization.

**Methods:** Rectal swabs were collected from patients hospitalized at the National Trauma Center (NTC), Mongolia, at the time of admission and after 14 days of hospitalization as has been detailed on our previous study. GN-MDRO antibiotic resistance was determined using EUCAST standards, and resistance genes were detected using multiplex PCR.

**Results:** A total of 158 patients were screened, and baseline colonization rate at admission was 29.1% (46/158). The rate went up to 69.9% (110/158) after 14 days of hospitalization ( $p < 0.001$ ). Of all participants, 74 patients (46.8%) screened GN-MDRO negative at admission acquired colonization by day 14. Other 36 patients (22.8%) maintained colonization that was screened positive at both time points. Only 38 patients (24.0%) remained free of GN-MDRO during hospitalization. There was a difference in GN-MDRO acquisition between these groups. Patients who were negative at admission acquired up to 3 GN-MDRO species, and there were 10 different species isolated. Conversely, patients who were screened positive at both time points had fairly homogenous isolates; up to 5 species of Enterobacterales were identified at admission and day 14 hospitalization. Overall, Enterobacterales were the dominant colonizers (61.4%, 97/158), and all Enterobacterales were resistant to cefotaxime as CTX-M resistance was our inclusion criteria.

**Conclusion:** GN-MDRO baseline colonization rate on admission was high and, alarmingly, doubled during hospitalization in the study area. Enterobacterales was the predominant colonizer and was highly resistant to 3rd generation cephalosporin. This data supports a need for an improved infection control policy including routine surveillance of the GN-MDROs and improved antibiotic stewardship program.

**Keywords:** multi-drug resistant organism, colonization, antibiotic resistance, hospital

## Introduction

An increasing prevalence and dissemination of gram-negative multi-drug resistant organisms (GN-MDRO) remains a worldwide public health concern. Mongolia is part of the Western Pacific region which has the second highest reported rate of community level faecal carriage of extended spectrum  $\beta$ -lactamase producing *Escherichia Coli*, second only to the South East Asia Region.<sup>1,2</sup> Both these regions are also reported to have a high rate of GN-MDRO hospital acquired infections (HAI).<sup>2</sup>

One of the sources of HAI, GN-MDROs cause more than 30% of HAI including blood stream infections and urinary tract infections.<sup>3,4</sup> Infections caused by Enterobacterales are often related with a high mortality, morbidity and delay in effective treatment.<sup>5,6</sup> Therefore developed countries have given much importance to the colonization of patients admitted to the hospital and established guidelines to screen drug-resistant organisms from rectal swab, groin, etc. depending on the species of the organism.<sup>7,8</sup> Further, the guideline recommends an organism- or resistance mechanism-specific (detected by the presence of specific resistance gene) approaches to reduce the risk of transmission and outbreaks within the hospital.<sup>7,8</sup> However none of these approaches are routinely practiced in our setting despite the presence of Ministerial decrees to screen some multi-drug resistant organisms and to monitor organisms that could transmit via specific procedures.<sup>9,10</sup> Therefore it was important to detect baseline colonization in our setting to monitor the fluctuations of the MDROs.

In an attempt to detect the baseline colonization in our setting, in our previous study, we screened GN-MDRO from patients admitted to the National Trauma Center (NTC) and Burn Center.<sup>11</sup> We reported an extremely high burden of GN-MDRO colonization at admission, which probably represents the high prevalence of community GN-MDRO. The publication has presented a data of 985 patients' whose swabs were collected at admission. However, it does not show how colonization changes during hospitalization. The present study analyzed the data of 158 patients, a subset of 985 patients from the initial study, who had swab samples at admission and an additional swab taken after 14 days of hospitalization. Objectives of the study were to determine the rate of GN-MDRO colonization during hospitalization and to describe dynamics of GN-MDRO species, antibiotic resistance genes at both time points. The outcome of the study could become the basis of the organism- or resistance mechanism-specific approaches for improved infection, prevention and control guidelines in participating hospital.

## Materials and Methods

### Study Population

A prospective cohort study was conducted between July and September 2014 at the NTC and we enrolled patients who stayed at least 14 days at the hospital as has been described previously.<sup>11</sup> Rectal swab samples were collected from 158 patients at admission and day 14 hospitalization. A patient with a positive GN-MDRO rectal

swab sample was considered to be GN-MDRO colonized. All patients were assigned to one of four categories based on the presence or absence of the GN-MDROs on admission and at day 14; the first group had no detectable GN-MDRO on admission and remained negative on day 14, the second group consisted of patients, who were negative on admission and positive on day 14, the third group of patients had positive swab samples at both time points and the fourth group consisted of patients, who were positive on admission and negative for GN-MDRO on day 14.

### Strain Identification, Antibiotic Susceptibility Testing and Resistance Gene Detection

Rectal swab samples were inoculated directly onto selective CHROMagar ESBL/KPC (bioMerieux, France) and suspicious colonies were sub-cultured on blood agar for strain identification. Strains were identified using MALDI-TOF MS or VITEK 2 (bioMerieux, France). Antibiotic susceptibility testing was performed using a disk diffusion method on Mueller-Hinton agar (Becton Dickinson, Germany) for the following antibiotics: cefotaxime, ceftazidime, ertapenem, imipenem, meropenem, ciprofloxacin, gentamicin, tobramycin, tigecycline, chloramphenicol, nitrofurantoin, trimethoprim-sulfamethoxazole and colistin. European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used to interpret the results (Clinical breakpoints – bacteria v 4.0, Disc diffusion manual v 4.0). In a case of phenotypic susceptibility test mismatch with PCR test, confirmatory tests were performed (combined disk diffusion test, MIC gradient strip test and/or a modified Hodge test) to confirm the presence of an ESBL and/or carbapenemase. Conventional and real-time multiplex PCRs were performed to detect the extended spectrum beta lactamase-, AmpC beta-lactamase- and carbapenemase-encoding resistance genes that have been detailed in paper by Baljin et al.<sup>11</sup>

### Statistical Analysis

Preliminary analysis has been done using Microsoft excel and advanced statistical analyses were performed using SPSS 22.0 software. McNemar test was used to compare paired swab samples taken at admission and after 14 days of hospitalization to calculate the GN-MDRO and *E. coli* colonization rate, respectively. Mean age and gender variance of all 4 groups have been calculated using one way analysis of variance and

**Table 1** Characteristics of Gram-Negative Multi-drug Resistant Organism Colonized Patients

Characteristics	Group 1 Patients	Group 2 Patients	Group 3 Patients	Group 4 Patients	p value
Patients (n=158, 100%)*	38 (24.1)	74 (46.8)	36 (22.8)	10 (6.3)	<0.001
Age, years (mean, SD)#	43, 17.0	40, 14.8	33, 12.8	41, 9.4	0.027
Age, years (median, min, max)	42, 17, 82	38, 17, 75	29, 14, 68	45, 27, 52	
Female gender (%)#	42.1	35.1	36.1	50.0	0.754

**Notes:** Group 1 – patients remained free of colonization and screened negative at admission and day 14 hospitalization; Group 2 – patients who acquired colonization during hospitalization and screened negative at admission and positive by day 14; Group 3 – patients who were colonized throughout the hospitalization and screened positive at admission and at day 14; Group 4 – patients who were colonized at admission screened negative at day 14 hospitalization; \*McNemar paired test was used to calculate p value. #One way variance analysis done to calculate p value.

a p-value of <0.05 was considered statistically significant. All percentages were reported with 1 decimal place.

## Results

### Patient Characteristics and Colonization Rate at Admission and Day 14 Hospitalization

The 158 patients were divided into 4 groups based on the presence or absence of GN-MDRO at admission and at day 14 hospitalization. The mean age of group 2 and 3 patients were younger than other groups ( $p<0.027$ ) (Table 1). There was no difference in gender between 4 groups. However more males were belonged to group 2 and 3 who acquired GN-MDRO during hospitalization.

There were 38 patients in group 1 (24.1%) who remained free of colonization throughout the hospitalization and had no detectable GN-MDRO on admission nor on day 14 (Supplementary Table 1). Group two 74 (46.8%) patients were negative at admission and were GN-MDRO carriers by day 14. Group three 36 patients (22.8%) were positive for MDRO at both time points and thus maintained the GN-MDRO colonization during hospitalization ( $p<0.001$ ). The baseline GN-MDRO colonization rate on admission was 29.1% (46/158) and the rate increased up to 69.6% (110/158) by day 14 of hospitalization ( $p<0.001$ ). On the other hand, GN-MDRO acquisition rate during hospitalization was 40.5%.

### Distribution of GN-MDRO Across Different Units on Day 14

On day 14, 133 GN-MDRO isolates were collected from 110 patients (69.6%, 110/158). Eleven different species of GN-MDROs were detected on day 14. Other than non-fermenting *Acinetobacter baumannii*, all species were belonged to Enterobacterales. The most prevalent species was *E. coli* and the percentage of patients carrying CTX-M-producing *E. coli* was increased from 27.8% (44/158)

on admission to 54.6% (86/158) by day 14 ( $p<0.001$ ) (Supplementary Table 2). The majority of GN-MDROs were isolated in 3 of the 4 units (88.0%, 117/133), the highest being the traumatic brain and spine injury unit (33.1%) followed by the bone and joints unit (30.8%) (Table 2). Up to 6 different species of GN-MDRO were present in a single unit. Predominant CTX-M producing *E. coli* (65.4%, 87/133) was present in all units.

### Antibiogram of GN-MDROs Acquired at Day 14 Hospitalization

There were 88 GN-MDROs isolated from 74 patients at day 14 who were not colonized at admission. Enterobacterales were dominant (96.6%, 85/88) and were fully resistant to cefotaxime. Non- $\beta$ -lactam antibiotics resistance was moderate to high, for example resistance to trimethoprim-sulfamethoxazole was 80.7% (71/88) and tobramycin was 42.4% (36/88). Resistance to carbapenem antibiotics was rare and only 1 *E. coli* isolate was determined to be ertapenem resistant. The remaining 3 isolates belonged to *A. baumannii* and were fully susceptible to colistin and resistant to the other 4 antibiotics (Table 3).

### Acquisition of New GN-MDRO Species at Day 14

A total of 99 patients (62.6%, 99/158) that belonged to group 2 and 3 acquired a GN-MDRO by day 14 and overall Enterobacterales were the most prevalent colonizer (61.4%, 97/158) in both groups.

Of the isolated 10 different species of GN-MDRO from group two, 9 belonged to Enterobacterales and one was *A. baumannii* (Table 4). The most prevalent GN-MDRO of group 2 was CTX-M-9- and CTX-M-1-producing *E. coli* (37.8%, 28/74 and 31.0% 23/74), respectively. One patient was colonized with *E. coli* carrying both  $bla_{CTX-M-1}$  and  $bla_{CTX-M-9}$  genes and another patient was colonized with  $bla_{OXA-51-58}$ -carrying *A. baumannii*. The co-colonization rate

**Table 2** Distribution of GN-MDRO Species Across Different Hospital Units at Day 14 Hospitalization

GN-MDRO Species Isolated at Day 14	Traumatic Brain and Spine Injury n (%)	Bone and Joints Unit n (%)	Polytrauma Unit n (%)	Hand and Microsurgery Unit n (%)	Total Acquisitions n (%)
<i>Escherichia coli</i>	30 (33.3)	27 (27.6)	19 (21.8)	11 (12.6)	87 (100)
<i>Enterobacter cloacae</i>	5 (29.4)	5 (29.4)	7 (41.2)		17 (100)
<i>Klebsiella pneumoniae</i>	4 (26.7)	7 (46.7)	2 (13.3)	2 (13.3)	15 (100)
<i>Acinetobacter baumannii</i>		2 (40)	2 (40)	1 (20)	5 (100)
<i>Citrobacter spp.</i>	1 (50)			1 (50)	2 (100)
<i>Citrobacter freundii</i>	2 (100)				2 (100)
<i>Citrobacter braakii</i>			1 (100)		1 (100)
<i>Klebsiella oxytoca</i>	1 (100)				1 (100)
<i>Enterobacter aerogenes</i>	1 (100)				1 (100)
<i>Proteus mirabilis</i>			1 (100)		1 (100)
<i>Raoultella ornithinolytica</i>				1 (100)	1 (100)
<b>Total</b>	<b>44 (33.1)</b>	<b>41 (30.8)</b>	<b>32 (24.1)</b>	<b>16 (12.0)</b>	<b>133 (100)</b>

**Abbreviation:** GN-MDRO, gram-negative multi-drug resistant organism.

**Table 3** Antibiotic Resistance of Newly Acquired GN-MDROs at Day 14 Hospitalization

Antibiotics	All Enterobacteriaceae (n = 85)	CTX-M Positive <i>E. coli</i> (n = 53)	CTX-M Positive <i>K. pneumoniae</i> (n = 9)	CTX-M Positive <i>E. cloacae</i> (n = 11)	<i>Acinetobacter baumannii</i> (n = 3)
Cefotaxime	98.8	100	100	100	–
Ceftazidime	49.4	39.6	55.6	90.9	–
Meropenem	0	0	0	0	33.3
Imipenem	0	0	0	0	33.3
Ertapenem	1.2	0	0	9.1	–
Gentamicin	62.4	54.7	100	72.7	100
Tobramycin	42.4	30.2	77.8	72.7	100
Ciprofloxacin	44.7	47.2	44.4	45.5	100
Trimethoprim-sulfamethoxazole	80.0	77.4	100	90.9	100
Nitrofurantoin	–	5.7	–	–	–
Tigecycline	–	0	–	–	–
Chloramphenicol	48.2	32.0	66.7	90.9	–
Colistin	ND	ND	ND	ND	0

**Abbreviation:** GN-MDRO, gram-negative multi-drug resistant organism.

for patients acquiring >1 GN-MDRO was 17.6% (13/74). One patient from group 2 (2.7% 1/74) had acquired 3 different species and 12 patients (16.2%, 12/74) had acquired 2 different species. Enterobacteriales carrying CTX-M-1 was the predominant co-colonizer (84.6%, 11/13).

## Changes of GN-MDRO Structure During Hospitalization

There was a major change in GN-MDRO structure for group 3 patients who maintained the colonization throughout the hospitalization. Twenty five patients (69.4%, 25/36) had different GN-MDRO species and/or antibiotic resistance genes at day

14 than were present at admission while the other 11 patients (30.6%, 11/36) retained the same species and resistance genes at both time points (Table 5).

At admission, GN-MDRO species was homogenous with only 4 GN-MDRO species identified. CTX-M-1 producing *E. coli* was the prevalent colonizer (52.8%, 19/36) followed by CTX-M-9 producing *E. coli* (38.9%, 14/36). However by day 14 hospitalization, there were 5 different species identified that included non-fermenting *A. baumannii* (5.5%, 2/36). The rate of CTX-M-9 producing *E. coli* rose to 55.5% (20/36) and CTX-M-1 producing *E. coli* was down to 36.1% (13/36) as compared to admission. The co-colonization rate for patients acquiring



**Table 5** Most of GN-MDRO Colonized Patients at Admission Acquired New GN-MDRO Species and or Genes by Day 14

Total Patients (n=36)	GN-MDRO Colonization at Admission			GN-MDRO Colonization at Day 14
<b>25 (69.4%) patients acquired new GN-MDROs</b>				
<b>1 patient acquired 3 GN-MDROs</b>				
1	<i>E. coli</i> (CTX-M-1)		→	<i>E. coli</i> (CTX-M-1) <i>E. coli</i> (CTX-M-9) <i>A. baumannii</i> (OXA-51)
<b>6 patients acquired 2 GN-MDROs</b>				
2	<i>E. coli</i> (CTX-M-1)		→	<i>E. coli</i> (CTX-M-1) <i>K. pneumoniae</i> (CTX-M-1)
1	<i>E. coli</i> (CTX-M-1)		→	<i>E. coli</i> (CTX-M-9) <i>K. pneumoniae</i> (CTX-M-9)
1	<i>E. coli</i> (CTX-M-9)		→	<i>E. coli</i> (CTX-M-neg) <i>E. cloacae</i> (CTX-M-neg)
1	<i>E. coli</i> (CTX-M-1)		→	<i>E. coli</i> (CTX-M-9) <i>R. ornithinolytica</i> (CTX-M-9)
1	<i>E. coli</i> (CTX-M-9)		→	<i>E. coli</i> (CTX-M-9) <i>A. baumannii</i> (OXA-51)
<b>18 patients acquired 1 GN-MDRO</b>				
8	<i>E. coli</i> (CTX-M-1)		→	<i>E. coli</i> (CTX-M-9)
4	<i>E. coli</i> (CTX-M-9)		→	<i>E. coli</i> (CTX-M-1)
1	<i>E. coli</i> (CTX-M-1)		→	<i>E. cloacae</i> (CTX-M-1)
1	<i>E. coli</i> (CTX-M-9)		→	<i>K. pneumoniae</i> (CTX-M-1)
1	<i>E. coli</i> (CTX-M-9)		→	<i>E. coli</i> (CTX-M-2)
1	<i>E. cloacae</i> (CTX-M-neg)		→	<i>E. coli</i> (CTX-M-9)
1	<i>K. pneumoniae</i> (CTX-M-1)		→	<i>E. coli</i> (CTX-M-1)
1	<i>K. oxytoca</i> (CTX-M-9)		→	<i>E. coli</i> (CTX-M-9)
<b>11 (30.6%) patients retained same GN-MDROs</b>				
6	<i>E. coli</i> (CTX-M-9)		→	<i>E. coli</i> (CTX-M-9)
5	<i>E. coli</i> (CTX-M-1)		→	<i>E. coli</i> (CTX-M-1)

**Abbreviation:** GN-MDRO, gram-negative multi-drug resistant organism.

Study participants' mean age was significantly different. Especially patients who acquired- (group 2) and maintained- (group 3) GN-MDRO during hospitalization was younger than the patients who remained negative during hospitalization (group 1). Although the gender did not differ significantly, male patients were prone to GN-MDRO colonization. Therefore it is important to pay special attention to young and male patients when admitted to the hospital and screen for GN-MDRO. In addition, the fact that: 1) patients screened negative at admission and acquired up to 3 GN-MDRO species (group 2 patients); and 2) patients switching species during

hospitalization (group 3 patients) warrants continued patient screening while at the hospital. Especially at day 14, the GN-MDRO burden was high in all 4 units of the NTC and there were 11 different GN-MDRO species present. Also 6 different GN-MDRO species co-circulating in one unit was worrisome, especially NTC does not conduct routine surveillance of the drug-resistant bacteria. From a hospital perspective, it is poor management of infection control and prevention and it is known that the environment including inanimate objects and hospital staff can harbor various gram-negative drug resistant bacteria.<sup>23,24</sup> In addition, high resistance to various antibiotics has been

observed in our study. Resistance to 3rd generation cephalosporin was moderate to high for Enterobacterales. Carbapenem resistance was rare and could be offered for serious cases. This finding prompts to update antimicrobial guideline to direct appropriate agents with the right regimen for individual clinical cases.<sup>5,6</sup>

Of the 11 different species detected at day 14, 10 species belonged to Enterobacterales; CTX-M producing *E. coli* was the most prevalent species however its rate was lower than in other high prevalence setting (53.1% vs. 94.9%).<sup>25</sup> Being colonized with extended spectrum  $\beta$ -lactamase *E. coli* increases the risk of infections such as blood stream infection and reversely, underlying disease increases the risk of acquisition of *E. coli*.<sup>26,27</sup> Therefore it is important to take an organism-specific approach in the participating hospital including active screening of these organisms on admission.<sup>5,6</sup> Concerningly *A. baumannii* was detected in polytrauma and bone and joints unit and patients admitting to these facilities should be prioritized for screening.

While hospitalized, patients with no- or existing GN-MDRO colonization had the same propensity for acquiring more than 1 bacterial species (17.6% vs. 19.4%). CTX-M-1 carrying Enterobacterales were the major co-colonizer for the patients who had no pre-existing colonization. However it was different for patients with underlying rectal colonization in whom, CTX-M-9 was the major co-colonizer. A recent study showed that being colonized with a MDRO considerably increases the risk of subsequent colonization of other multi-drug resistant organisms.<sup>28</sup> The same paper by Wang et al showed that *P. mirabilis* colonization increased the acquisition of *A. baumannii*, methicillin resistant *S. aureus* and vancomycin resistant enterococci by least 2-times. Vice versa, a pre-existing colonization with *E. coli*, *A. baumannii* and *P. aeruginosa* increased the acquisition of *P. mirabilis* by 2-times.<sup>28</sup> In our study, interestingly a single patient had acquired *P. mirabilis* and was co-colonized with bla<sub>CTX-M-1-9</sub> producing *E. coli*.

Previous studies have established that MDRO colonization increases the length of hospital stay, treatment cost and mortality rate.<sup>26,29,30</sup> A study conducted by Mutters et al showed that MDRO-colonized trauma patients stayed at least 2-times longer than all other colonized patients.<sup>31</sup> Thus our findings highlight the importance of improving antibiotic stewardship and establishing routine surveillance for GN-MDROs. If the international guidelines and evidence backed interventions are strictly adhered to,

a reduction of GN-MDRO burden in a healthcare setting can be expected.<sup>32,33</sup>

Some limitations of the study must be noted. The rectal swab was collected within 72 hours upon admission to the hospital and there is a chance that colonization occurred before the screening. Nevertheless we undertook an anonymous questionnaire from a subset of patients and half of the patients reported having antibiotics in last 6 months (data not shown). Thus pre-selection of a drug-resistant organism in the gut may have already occurred prior to the hospital admission. Therefore our finding GN-MDRO high admission rate could reflect community prevalence of GN-MDRO. Another limitation was that clinical samples from the same cohort were not collected and thus we were unable to establish a relationship between colonization and infection. However, there are many studies that showed isolation of Enterobacterales, non-fermenting *P. aeruginosa* and *A. baumannii* from clinical samples and established infection from rectal colonization.<sup>34-37</sup> Some studies from Mongolia also showed presence of extended-spectrum  $\beta$ -lactamase-producing *E. coli*, *Klebsiella* spp. and *A. baumannii* from clinical samples.<sup>38,39</sup> Therefore the relationship of colonization and infection needs to be further explored in Mongolia.

## Conclusion

We report a high GN-MDRO colonization rate at the time of admission and that the colonization rate doubled during hospitalization. Enterobacterales were predominant colonizers and had increased resistance to third generation cephalosporin. Improved antibiotic stewardship and a targeted routine screening and surveillance program is necessary to contain the dissemination of the drug-resistant bacteria in the study area.

## Ethics Approval and Consent to Participate

Ethical approval was obtained from the Research Ethics Committee of the Mongolian National University of Medical Sciences (No. 14-15/1A). Informed consent was obtained from all patients (if minor from the parent) participating in the study and the study was conducted in accordance with the Declaration of Helsinki.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

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