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Original Article

Prevalence and risk factors of MRSA, ESBL and MDR bacterial colonization upon admission to an Egyptian medical ICU

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Abstract

Introduction: Bacterial colonization of the skin and mucous membranes of intensive care unit (ICU) patients with virulent organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL) producers, and multidrug-resistant Gram-negative bacteria (MDR-GNB) frequently results in life-threatening infections. Universal screening of ICU patients upon admission has been suggested. The aim of the current study was to evaluate the prevalence and pattern of MRSA, ESBL, and MDR-GNB colonization in patients upon admission to an Egyptian medical ICU, along with the related demographic and clinical risk factors.

Methodology: Throat, axillary, and groin swabs were obtained from all study participants in addition to rectal swabs from consenting patients. These swabs were screened for MRSA, ESBL, and MDR-GNB.

Results: Of the patients included in the study, 33%, 13%, and 63% were colonized with ESBL, MDR-GNB, and MRSA organisms, respectively. Those suffering from a more severe disease with a simplified acute physiology score II (SAPS II) > 29 demonstrated higher levels of MDR-GNB colonization upon admission, while MDR-GNB or ESBL colonization upon admission was associated with higher ICU mortality.

Conclusions: Colonization of ICU patients with superbugs upon admission has an impact on outcome and mortality. In this Egyptian example, colonization rates were higher than in other literature reports, demonstrating the need for routine screening and decolonization, if applicable.

Key words: ICU; colonization; MDR-GNB; MRSA; ESBL

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Introduction

Hospital-acquired (nosocomial) infection is a worldwide problem. Intensive care unit (ICU) patients are commonly affected by nosocomial infections caused by aggressive pathogens. Much interest is now directed at the study of groups of micro-organisms that are resistant to multiple antimicrobials (superbugs), which are increasing at an alarming rate in the ICU setting with consequent high morbidity, mortality, and treatment costs [1].

These superbugs include methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase producers (ESBL), multidrug-resistant Gram-negative bacteria (MDR-GNB), and vancomycin-resistant *Enterococcus* (VRE). MRSA had been observed to be a major cause of severe nosocomial infections since the 1960s, and its resistance to a variety of antibiotics has contributed to the associated high mortality [2]. In addition to the known involvement of Gram-positive organisms and fungi in sepsis, Gram-negative organisms are important causes of nosocomial infections such as pneumonia, urinary tract infections, abdominal sepsis, and even bloodstream infections [3,4]. ESBL organisms are associated with high morbidity and mortality, especially in ICU patients with multiple comorbidities due to the limited therapeutic choices [5].

Antibiotic resistance to MDR-GNB lead the Infectious Diseases Society of America (IDSA) to announce that the unavailability of therapeutic options and the lack of reports of future under-development drugs, in its campaign “Bad Bugs, No Drugs” [6]. The IDSA recognized the increased need for the production of novel antibiotics that are effective against the MDR-GNB, and so it launched the “10 x ‘20” initiative in 2010 to produce ten new antibiotics against these organisms by 2020 [7]. On World Health Day 2011, the IDSA presented a policy statement titled “Combating Antimicrobial Resistance: Policy Recommendations to Save Lives”, which stressed on the problem of growing antibiotic resistance and lack of new antibiotics [8]. The collective results of those recommendations and

policies resulted in major advances in the field of research and drug development.

In the last two years, many drugs (such as ceftolozane/tazobactam and ceftazidime/avibactam) that are effective against MDR Gram-negative organisms were approved by Food and Drug Administration (FDA) [9], while others (such as imipenem/MK-7655 and eravacycline) were fast-tracked by the FDA for approval in the near future.

Bacterial colonization of the skin and mucous membranes of humans with those superbugs usually precedes serious infections. Colonizers usually remain harmless or become chronic colonizers, or they are cleared spontaneously. However, in some people, when the protective barriers of skin and mucous membranes, these organisms invade the body and infection occurs [10].

Accordingly, universal screening of ICU patients upon admission for colonization by antibiotic-resistant organisms and the application of contact precautions and isolation of colonized patients in single rooms has been suggested [11]. This could prevent the spread of these organisms to other ICU patients who are probably seriously ill and vulnerable to drastic consequences in case of transmission. Despite the rationale behind the screening programs, methodological shortcomings of the previously published studies and inadequate reporting made accurate assessment of the cost effectiveness of such screening programs and contact precautions difficult [12]. Huskins *et al*. reported that screening ICU patients upon admission for the presence of MRSA and VRE and applying contact precautions for carriers did not result in a reduction of ICU-acquired infection with these organisms among ICU patients [13]. A recent review of literature published by the Agency for Healthcare Research and Quality in the United States found evidence that universal MRSA carriage screening upon admission programs may reduce the risk of MRSA infections. However, evidence was weak and insufficient to support screening programs [14]. Most of the published studies were experimental or observational studies with before/after design, and the only randomized controlled trial showed no favorable effect of screening programs. The methodologies of the examined studies were defective since they did not consider changes in the incidence of MRSA infections over time, the use of other measures to reduce incidence of these infections (such as hand washing, decolonization, and availability of private patient rooms among other limitations), making it difficult to know whether the change in incidence of MRSA infections was related to screening or to the previously mentioned confounding variables. In addition, there was inadequate reporting of the results of the screening programs, which may have led to a publication bias since the data reported in literature is just a fraction of the much bigger data of screening programs utilized in hospitals [14].

There is a variety of scoring system models used to assess severity of critical illness and predicted mortality among ICU patients. The acute physiology and chronic health evaluation (APACHE) was first developed in 1981 with data from two American ICUs. The simplified APACHE II that was released in 1985 included data from 13 American hospitals, relying on assessing the worst value of 12 variables obtained in the first 24 hours of hospital stay to create the acute physiology score (APS); the addition of chronic health evaluation, age, and urgency of admission provides the total APACHE score and a probability of mortality. APACHE III was released in 1991, developed with data from an expanded set of 40 American hospitals and an APS comprising 18 variables [15].

In 1985, the simplified acute physiology score (SAPS) was released as an alternative to the APACHE score, employing 14 of the original 34 variables used in the APACHE system. This was followed by the release of SAPS II and SAPS III, which included data of only 12 variables from the first 24 hours in the ICU. SAPS II included data about age, chronic illnesses, and type of admission [16]. Beck *et al*. studied the use of SAPS II and APACHE II and III prognostic models in 16,646 adult intensive care patients in the United Kingdom. Validation showed that the three scoring systems showed similar good discrimination, but imperfect calibration [17]. An Egyptian study done on 837 ICU patients that studied the predictive value of three different scoring systems (APACHE IV, SAPS II, and mortality probability model [MPM]) to assess severity of critical illness and predicted mortality found that SAPS II was superior to the other models in predicting outcomes in the studied patients and accordingly suggested that SAPS II is the best scoring system to predict outcomes in Egyptian ICU patients [18].

The aim of the current study was to evaluate the prevalence and pattern of MRSA, ESBL, and MDR-GNB in patients upon admission to an Egyptian medical ICU, as well related demographic and clinical risk factors.

Methodology

Setting

The current prospective study was conducted in an eleven-bed medical ICU in Kasr-ElAini University

Hospital, Cairo, Egypt. The hospital is one of the biggest tertiary centers in Egypt, and its ICUs receive patients from the emergency department (ED) and wards of the same hospital as well as referrals from other hospitals. Ethical approval was obtained from the ethical committee of Kasr-ElAini University Hospital.

Study population

The study involved patients admitted to the medical ICU during the period from 1 January to 1 February 2013. Informed consent was taken from the study participants or from their next of kin if the patients were considered incompetent to consent.

Data collection

Demographic characteristics, source of ICU admission, previous hospitalization, previous antibiotic therapy, comorbidities, length of hospital stay, and outcome were recorded. Furthermore, results of physical examination and multiple laboratory parameters were recorded and analyzed to calculate the SAPS II in order to assess the severity of the critical illness.

Swabs enriched on thioglycolate broth were obtained to assess bacterial colonization during the first 24 hours of ICU admission from all study participants. Throat, axillary, and groin swabs were obtained from all subjects (n = 99), but only 44 patients of those included in the study agreed to have a rectal swab performed.

Microbiological procedures

MRSA

Samples were cultured on MRSA chromagar (CHROMagar Microbiology, Paris, France) and incubated at 37°C for 24 hours. CHROMagar MRSA plates were examined for mauve MRSA colonies; other colors were disregarded. Quality control was done for MRSA chromagar using MRSA ATCC 43300, *Staphylococcus aureus* ATCC 25923.

ESBL and MDR-GNB

Samples were cultured on MacConkey agar and incubated at 37°C for 24 hours. Plates were examined, and microbial growth was identified using standard procedures [19]. Lactose fermenter colonies were subjected to conventional biochemical reaction in the form of triple sugar iron, motility indole ornithine, lysine iron agar, urease, and citrate. Non-lactose fermenter colonies were subject to oxidase; if a negative Gram stain was done to exclude *Acinetobacter* (coccobacilli) and Gram-negative bacilli were found, the previous biochemical reactions were performed. Antimicrobial susceptibility of Gram-negative isolates was determined by the standard Kirby-Bauer disk diffusion method. Antibiotic disks included penicillin (10 μg), ampicillin (10 μg), ceftriaxone (30 μg), cefotaxime (30 μg), ceftazidime (30 μg), cefepime (30 μg), amoxicillin-clavulanic acid (20/10 μg), piperacillin-tazobactam (100/10 μg), imipenem (10 μg), meropenem (10 μg), ciprofloxacin (5 μg), levofloxacin (5 μg), amikacin (30 μg), gentamicin (10 μg), and rifampicin (5 μg).

All steps were performed according to the Clinical and Laboratory Standards Institute (CLSI)'s 2013 recommendations (performance standards for antimicrobial disk susceptibility tests; approved standard), using Muller-Hinton agar [20]. Disk zone diameters were interpreted according to the CLSI 2013 recommendations for the chosen antibiotics, categorized according to the breakpoints for disk diffusion testing as sensitive, resistant or, intermediate [20]. ESBL producers were confirmed phenotypically by the double-disk synergy test (double-disk approximation) using clavulanic acid and third-generation cephalosporins. Disks of third-generation cephalosporins and amoxicillin-clavulanic acid were kept 15–20 mm apart, center to center, on inoculated Muller-Hinton agar. The plates were incubated at 35°C–37°C for 18–24 hours. A clear extension of the edge of the inhibition zone of any of the third-generation cephalosporins towards the amoxicillin-clavulanic acid disk was interpreted as positive for ESBL production. Quality control for culture plates and antibiotic susceptibility was performed using *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Staphylococcus aureus* ATCC 25923.

Definitions

Patients were considered to be colonized by any of the organisms studied if one or more of those organisms was/were isolated from one or more of the swabbed sites. MDR-GNB was defined as acquired non-susceptibility to at least one agent of three or more antimicrobial categories [21].

Statistical analysis

Data were statistically analyzed, described in terms of mean ± standard deviation (± SD), frequencies (number of cases), and percentages when appropriate. For comparing categorical data, the Chi-square ($\chi 2$) test was performed. A probability value (p value) less than 0.05 was considered statistically significant. All

statistical calculations were done using the computer programs Microsoft Excel 2010 and SPSS version 21 for Microsoft Windows.

Results

Demographic data of patients

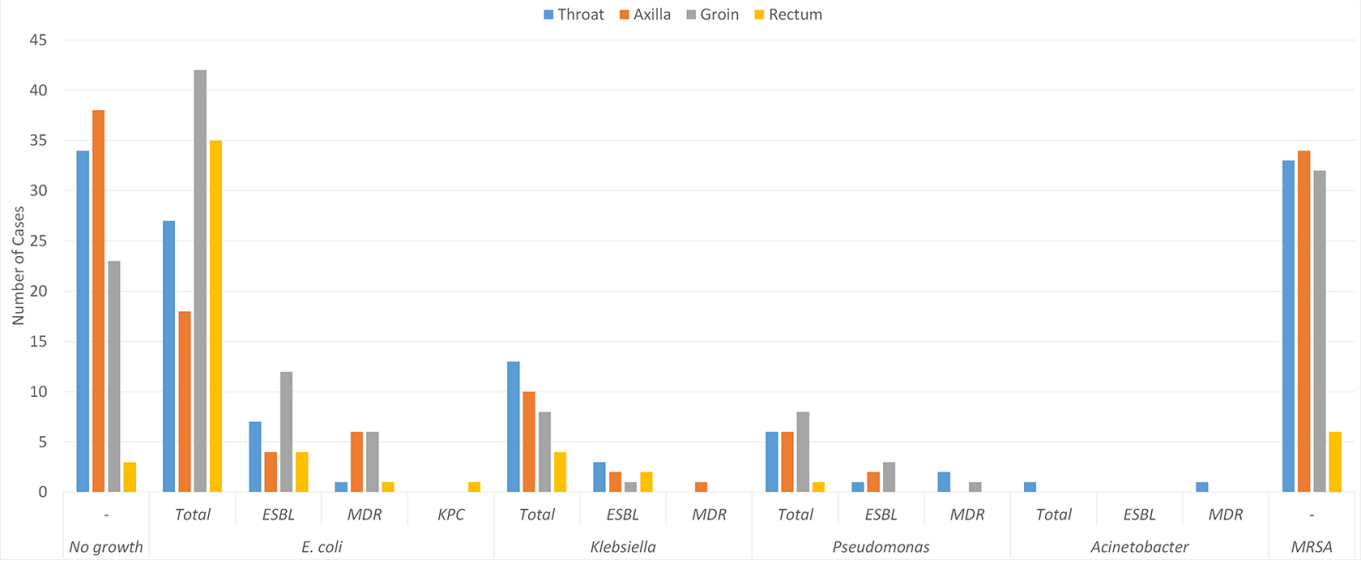
A total of 92 patients, 49 females and 43 males, were included in this study. Age range was 18–84 years, and mean was 47.75 ± 17. Of the studied patients, 74.5% were admitted from the same hospital's ER, 21.9% were referred from same hospital's wards, and 3.6% were referred from other hospitals' ICUs. Thirty-one patients (33.7%) had been hospitalized in the previous three months, and 20 patients (21.7%) came in for regular dialysis in the preceding month. Average hospital stay was 7.12 ± 9 days, and range was 1–70 days. Regarding antibiotic therapy prior to medical ICU admission, 20 patients (21.8%) received antibiotics in the previous three months, 40 patients (43.5%) did not receive antibiotics, and the medication history of 32 patients (34.7%) was unclear. SAPS II score was an average of 35.63 ± 21.66, and range of 6–106 points. Mortality rate was 38% (n = 35). The rest of the clinical characteristics of the studied patients are presented in Table 1.

Table 1. Clinical characteristics of the studied patients

Parameter	Value	Percent
Mean age (years)	47.75± 17	
Hospital stay (days)	7.12 ± 9	
SAPS II score (points)	35.63 ± 21.66	
Males	43	46.7%
Previous hospitalization	31	33.7%
Previous antibiotic therapy	20	21.7%
Respiratory diseases	7	7.6%
Diabetes mellitus	29	31.5%
Heart diseases	12	13%
Neurologic disease	10	10.9%
Hematologic malignancy	1 (1.1%)	1.1%
Solid organ malignancy	6	6.5%
Chronic renal failure on dialysis	20	21.7%
Chronic liver disease	9	10%
Corticosteroid therapy	10	10.9%
Current chemotherapy	0	0%
Immunosuppressive	3	3.3%
Surgical wounds or ulcers	14	15.4%
Mortality	35	38%

SAPS II: simplified acute physiology score II

Figure 1. Culture results of the swabs taken from the study participants



Prevalence and pattern of bacterial colonization upon ICU admission

Thirty-one of the studied patients (33.7%) were colonized with one or more of ESBL organisms, 12 patients (13%) were colonized with one or more of MDR-GNB, and 58 (63%) were colonized by MRSA bacteria at one or more of the swabbed sites. From among the colonizing organisms, 65% of the ESBL organisms and 74% of the MDR-GNB belonged to the *E. coli* species. The detailed results of the cultures from different swabbed sites obtained from the study participants are presented in Figure 1 and Table 2.

Risk factors for bacterial colonization upon ICU admission

Univariate analysis of the risk factors related to bacterial colonization showed those younger than 65 years of age suffered more MRSA colonization upon admission (odds ratio [OR] = 0.28; confidence interval [CI] = 0.09–0.83; p = 0.019). Those with a SAPS II

Table 2. Culture results of the swabs taken from the study participants

		Throat	Axilla	Groin	Rectum
No growth		34 (37%)	38 (41.3%)	23 (25%)	3 (6.8%)
E. coli	Total	27 (29.3%)	18 (19.56%)	42 (45.65%)	35 (38%)
	ESBL	7	4	12	4
	MDR	1	6	6	1
	KPC	0	0	0	1
Klebsiella	Total	13 (14.1%)	10 (10.86%)	8 (8.69%)	4 (4.34%)
	ESBL	3	2	1	2
	MDR	0	1	0	0
Pseudomonas	Total	6 (6.52%)	6 (6.52%)	8 (8.69%)	1 (1.08%)
	ESBL	1	2	3	0
	MDR	2	0	1	0
Acinetobacter	Total	1 (1.08%)	0 (0%)	0 (0%)	0 (0%)
	ESBL	0	0	0	0
	MDR	1	0	0	0
MRSA		33 (35.9%)	34 (37%)	32 (34.8%)	6 (13.6%)

ESBL: extended-spectrum beta-lactamase; MDR: multidrug resistant; KPC: *Klebsiella pneumoniae* carbapenemase; MRSA: methicillin-resistant *Staphylococcus aureus*

Table 3. Univariate analysis of risk factors related to bacterial colonization upon intensive care unit admission

Risk factor	MDR colonization				ESBL colonization				MRSA colonization			
	Present (n)	Absent (n)	Odds ratio	P value	Present (n)	Absent (n)	Odds ratio	P value	Present (n)	Absent (n)	Odds ratio	P value
Age > 65 years	1	17	0.33	0.2	6	12	1.1	0.53	7	11	0.28	0.019*
Male	5	38	0.789	0.475	13	30	0.98	0.491	27	16	0.98	0.37
Previous hospitalization	4	29	1.2	0.514	11	22	1.4	0.316	22	11	1.3	0.352
Skin wounds or ulcers	2	12	1.1	0.58	8	6	3.6	0.3	9	5	1.06	0.58
Heart failure	0	12	1.1	0.166	4	8	1.1	0.562	9	3	1.89	0.28
Chronic liver disease	3	6	4	0.09	4	5	1.7	0.31	8	1	5.22	0.09
ESRD on dialysis	1	19	0.29	0.209	9	11	0.117	2.1	9	11	0.38	0.53
Diabetes mellitus	2	27	0.39	0.2	8	21	0.7	0.38	15	14	0.49	0.09
Corticosteroid therapy	3	7	2.4	0.12	2	8	0.5	0.331	5	5	0.54	0.28
Previous antibiotics	3	18	6.6	0.108	8	13	2.98	0.067	10	11	0.58	0.23
SAPS II > 29	10	43	4.3	0.049*	20	33	2.02	0.102	30	23	0.51	0.1
Mortality	9	26	6	0.008*	18	17	4.7	0.001*	22	13	1.05	0.551

MDR: multidrug resistant; ESBL: extended-spectrum beta-lactamase; MRSA: methicillin-resistant *Staphylococcus aureus*; ESRD: end-stage renal disease; SAPS II: simplified acute physiology score II.

score > 29 points had higher rates of MDR-GNB colonization (OR = 4.3; p = 0.049) (Table 3).

Bacterial colonization upon ICU admission and ICU mortality

Colonization with MDR-GNB and ESBL organisms upon ICU admission were associated with increased ICU mortality (OR = 6, CI = 1.4–24; and OR = 4.7, CI = 1.8–12.3, respectively) (Table 3).

Discussion

The current study showed that around one-third of the patients upon ICU admission were colonized with one or more ESBL Gram-negative organisms at one or more of the swabbed sites, with 63% of these ESBL organisms belonging to *E. coli* species, while around 13% were colonized with one or more of MDR-GNB at one or more of the swabbed sites. Review of previous studies shows that the prevalence of ESBL colonization upon ICU admission varied widely. In an Indian ICU study of 96 patients with swabs obtained from nasal, oral, and rectal regions, 5% of the studied patients were colonized with ESBL Gram-negative organisms upon ICU admission [22].

In the United States, the Maryland Medical Center study published in 2007 comprising more than 5,200 patients admitted to medical and surgical ICUs with perianal swabs obtained on admission showed that only 117 (2.25%) were colonized with *E. coli* and *Klebsiella* ESBL bacteria [23]. More recently, a French study showed that 15% of 531 patients admitted to ICUs grew ESBL organisms in rectal swabs, with 62% of those organisms belonging to *E. coli* [24]. A South Korean study published in 2014 reported that 28.2% of 347 patients demonstrated fecal carriage of ESBL organisms upon ICU admission [25].

The percentage of patients colonized with ESBL organisms in the current study is much higher than the percentages reported in Indian, American, and French studies, but closer to the results of the South Korean study. The percentage of ESBL organisms that belonged to *E. coli* in the current study was close to that reported in the French study. In contrast, there is a scarcity of data about colonization of ICU patients with MDR-GNB. Warren *et al*. reported that 5% of the patients admitted to a medical ICU in the United States grew MDR-GNB in their rectal swabs [26]. De Jonge *et al*. reported that 9% of patients, upon admission to a mixed medical and surgical ICU in the Netherlands, were colonized with MDR-GNB [27]. MDR-GNB colonization data in the current study are more closely related to those reported from the Netherlands than those reported from the United States. More than 60% of the patients in this study were colonized by MRSA in at least one of the sampled sites upon ICU admission. A French multicenter study performed in 2003 that examined nasal swabs from medical ICU patients and surgical wound swabs in surgical patients showed that only around 7% were colonized with MRSA on admission [28]. In 2011, an American study of patients admitted to Veterans Affairs hospitals, including more than 350,000 ICU patients from multiple centers all over the United States, reported that around 15% showed MRSA colonization in the nares [29]. In a more recent Indian study done in 2013 on 400 patients admitted to a multidisciplinary ICU, samples obtained from six sites showed that 22.5% of participants were colonized with MRSA [30].

Although the current study included a smaller number of patients than the previously reported studies, the detected percentage of MRSA colonization on ICU admission is far greater than in the aforementioned studies. This emphasizes the risk facing Egyptian ICUs and indicates the need for immediate control measures. However, this risk may not be exclusive to Egyptian ICUs and may threaten other geographic areas, considering that sampling from multiple sites (employed in the current study), including throat swabbing, is more accurate than single nasal swabbing to evaluate MRSA colonization [31], asserting the results of the current study and leaving the door open for further confirmation of the figures obtained from other regions. In addition to sites of swabbing, differences in the rates of colonization in various studies may be related to differences in the characteristics of the studied groups and the health and ethnic profiles of different geographical regions, among other factors. The current study further tried to detect possible risk factors related to colonization with these aggressive organisms upon ICU admission and the relationship between colonization and ICU mortality. Univariate analysis showed that upon admission, MRSA colonization was more likely with patients younger than 65 years of age, and that MDR-GNB colonization was related to the severity of the clinical illness upon admission (SAPS II score > 29).

In contradiction to the results of the current work, Lucet *et al*., in their multicenter study performed on 14 French ICUs, reported that being older than 60 years of age was among the risk factors for MRSA colonization upon ICU admission [32]. On the other hand, to our knowledge, there are no data in the English medical literature concerning the relationship between severity

of critical illness and bacterial colonization with the studied superbugs upon admission.

Based on univariate analysis, the current study showed that bacterial colonization with either ESBL or MDR organisms upon ICU admission was associated with increased ICU mortality. Again, to the best of our knowledge, there are no literature reports evaluating the effect of ESBL or MDR-GNB colonization upon ICU admission on ICU mortality. This could not be demonstrated for MRSA, possibly due to the limited number of the study participants, indicating further investigation of this finding. However, a study conducted in France and another in the United States reported that MRSA colonization upon admission to ICU did not affect ICU mortality [33,34], in accordance with the findings of the current study.

Surveillance studies are an important part of any infection control program, particularly with antimicrobial resistance spreading worldwide, notably more so in developing countries. To the best of our knowledge, this is the first study to explore the problem of bacterial colonization by organisms that are resistant to a variety of antibiotics upon admission to Egyptian medical ICUs. In addition, this may be the first study to explore the relationship between colonization with ESBL and MDR-GNB bacteria upon ICU admission and ICU mortality, and the relationship between MDR-GNB colonization upon ICU admission and critical illness severity.

Study limitations

This pilot study was an initial effort that will hopefully be followed by further larger national studies to explore this important topic and the launching of a national surveillance program. The current study has limitations, which include the limited number of study participants encountered within a one-month time frame, lack of prior power of the study/sample size calculation. Only medical patients were involved in the current study, so further studies in surgical ICUs are required to explore if prevalence and pattern of colonization upon admission differs between medical and surgical ICUs. This study did not use nasal swabbing, which is the routinely used method to screen for MRSA colonization in other studies; however, throat swabs used in the current study were reported to be more sensitive than nasal swabs in detecting MRSA colonization among ICU patients [30].

Furthermore, rectal swabs were obtained from only 44 (47.8%) of the study participants, which may have reduced our ability to assess intestinal colonization of the studied patients. Obtaining rectal swabs from all patients would have been ideal, but performing them without patients' consent would be a great breach of patients' rights. Finally, literature reports indicate that previous antibiotic therapy is a common cause of skin and mucous membrane multidrug-resistant bacteria. The current study failed to show that, and this may be attributed to absence of clear history regarding antibiotic therapy in around one-third of study participants, aided by the limited adoption of an electronic medical recording system in Egyptian hospitals.

Conclusions

Upon admission to an Egyptian medical ICU in a university hospital, 33%, 13%, and 63% of patients were colonized with ESBL, MDR-GNB, and MRSA organisms, respectively. MRSA colonization was higher among those younger than 65 years of age (OR = 0.28; CI 0.09–0.83), and those suffering of a more severe disease with a SAPS II score > 29 showed higher colonization with MDR-GNB (OR = 4.3). MDR-GNB or ESBL colonization upon admission was associated with higher ICU mortality (OR = 6, CI = 1.4–24; and OR = 4.7, CI = 1.8–12.3, respectively).

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