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MAJOR ARTICLE

Towards a Definition for Health Care–Associated Infection

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Background. Health care–associated infection (HcAI) is a term frequently used to describe community-onset infections likely to be caused by multidrug-resistant organisms (MDROs). The most frequently used definition was developed at Duke University Medical Center in 2002 (Duke-2002). Although some professional societies have based management recommendations on Duke-2002 (or modifications thereof), neither Duke-2002 nor other variations have had their performance measured.

Methods. A case–control study was conducted at Assaf Harofeh Medical Center (AHMC) of consecutive adult bloodstream infections (BSIs). A multivariable model was used to develop a prediction score for HcAI, measured by the presence of MDRO infection on admission. The performances of this new score and previously developed definitions at predicting MDRO infection on admission were measured.

Results. Of the 504 BSI patients enrolled, 315 had a BSI on admission and 189 had a nosocomial BSI. Patients with MDRO-BSI on admission (n = 100) resembled patients with nosocomial infections (n = 189) in terms of epidemiological characteristics, illness acuity, and outcomes more than patients with non-MDRO-BSI on admission (n = 215). The performances of both the newly developed score and the Duke-2002 definition to predict MDRO infection on admission were suboptimal (area under the receiver operating characteric curve, 0.76 and 0.68, respectively).

Conclusions. Although the term HcAI is frequently used, its definition does not perform well at predicting MDRO infection present on admission to the hospital. A validated score that calculates the risk of MDRO infection on admission is still needed to guide daily practice and improve patient outcomes.

Keywords. antimicrobial resistance; community acquired; epidemiology of infection acquisition; infection; multidrug resistant; nosocomial infection.

In the previous few decades, political agendas, economic considerations, and modern medical technologies have all contributed to dramatic changes in the structure of health care systems worldwide [1]. A major modern trend in health care delivery is that patients with complex comorbidities and invasive devices are now frequently managed either at home or in long-term care facilities (LTCFs) instead of in acute care hospitals [1, 2].

Multidrug-resistant organisms (MDROs) are among the most serious iatrogenic complications of modern medicine [3]. The burden imposed by these bacteria on individual patients and on public health is enormous [2]. The main independent predictors for acquisition of various MDROs are long-term institutionalization, older age, functional dependency, presence of permanent foreign invasive devices, recent invasive procedures, and recent exposure to antimicrobials [4, 5]. Most of these factors also signify health care exposure. Patients with substantial risk factors for MDROs often have multiple encounters with the hospital environment through frequent admissions, emergency room and outpatient visits, operative procedures, and outpatient therapy such as hemodialysis. Therefore, these health care–exposed patients serve as reservoirs for MDRO transmission [2].

The combination of significant health care affiliation among outpatients and increased movement between locations providing health care has resulted in a major shift in the epidemiology of MDROs in the past 2–3 decades [2]. These pathogens, formerly prevalent almost exclusively in nosocomial settings, and specifically in ICUs, have become prevalent among certain ambulatory populations with extensive recent exposures to health care settings [2].

This epidemiological shift has been documented among methicillin-resistant *Staphylococcus aureus* (MRSA) [6], extended-spectrum β-lactamase (ESBL)–producing *Enterobacteriaceae* [4], carbapenem-resistant *Enterobacteriaceae* (CRE) [7],

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vancomycin-resistant enterococci (VRE) [8], *Pseudomonas aeruginosa* [9], and *Acinetobacter baumannii* [10]. As a result, prescribing of appropriate antimicrobial agents, active against MDRO infections that are present at the time of admission to hospital, is frequently delayed [11–13]. Delay in the administration of appropriate antimicrobials is the strongest modifiable and independent predictor for mortality in severe sepsis [14].

In 2002, Friedman et al. from Duke University Medical Center (NC) proposed a new classification scheme for bloodstream infections (BSIs) incorporating community-acquired (CA), health care–associated (HcA), and nosocomial infections (Duke-2002) [15]. HcA infections (HcAIs) were defined as infections that are diagnosed in the first 48 hours of hospitalization in patients with at least 1 of several recent exposures, including intravenous (IV) therapy or other nursing care at home, hemodialysis, IV chemotherapy in the previous 30 days, hospitalization in an acute care hospital in the preceding 90 days, or residence in a nursing home or any LTCF. CA infections were those identified in the first 48 hours of hospitalization in patients without these exposures, whereas nosocomial BSIs had their onset 48 hours or more into the hospitalization [15].

HcA BSIs were shown to be similar to nosocomial BSIs in terms of the frequency of various comorbid conditions, source of infection, pathogens (including prevalence of certain MDROs), and mortality rate at follow-up [15].

A simplification of the Duke-2002 definition, the modified Duke-2002, consisted of any hospitalization (for 2 or more days) in the past year as the single defining criterion [16]. The Duke-2002 classification of infection and modifications thereof has subsequently been used both for selecting and recommending empiric treatment and for infection control surveillance purposes [16–19]. The Duke-2002 criteria were, however, set a priori, before study initiation, and their performances were not measured or analyzed for these indications [15]. These definitions, when used to create treatment guidelines particularly in the case of HcA pneumonia, may be flawed and potentially harmful because of the heterogeneity of the patient population [20].

Similarly, the Pitt bacteremia score, originally developed to predict the acuity of illness and as a prognostic marker specifically for Gram-negative sepsis [21], has been used to tailor empiric therapy and specifically anti-MDRO therapy among patients with higher scores (a score ≥4 was used as the breakpoint) [21]. However, as with HcA infection definitions, the performance of the Pitt score at predicting an MDRO has not been measured.

The aim of this study was to develop a new score-based definition of HcAI based on risk factors present on hospital admission and to compare its performance at predicting MBDO-BSI on admission against previous definitions.

METHODS

Study Design

A retrospective case–control study was conducted at the Assaf Harofeh Medical Center (AHMC) for a 7-month period (January 1 through July 31, 2013). AHMC is an 848-bed university-affiliated facility located in Zerifin, Israel.

The institution's ethics committee, acting in accordance with the Declaration of Helsinki, approved this study before its initiation.

Study Population

All consecutive adult patients (older than 18 years of age) admitted to AHMC with BSI during the study period were included. BSI was defined as bacteremia with a "true" pathogen [22], coupled with systemic inflammatory response syndrome (SIRS) [23]. Patients were included only once per infection episode. However, patients with repeat hospitalizations due to BSI caused by a different pathogen more than 1 month apart were treated as unique patients. The study cohort was divided into (1) BSI based on positive blood culture(s) drawn in the first 48 hours of hospitalization and (2) nosocomial BSI diagnosed after 48 hours into the hospitalization. BSIs based on positive blood cultures drawn in the first 48 hours of hospitalization were further divided into MDRO (cases) and non-MDRO (controls).

Multidrug-Resistant Organisms

In this study, MDROs were selected after review of bacterial pathogens from 2011–2012 at AHMC and were defined as microorganisms resistant (based on the Clinical and Laboratory Standards Institute [CLSI] and the European Committee on Antimicrobial Susceptibility Testing [EUCAST] established breakpoints) to 1 or more classes of antimicrobial agents recommended as firstline therapy [24]. MDROs included (1) MRSA; (2) ampicillin and/or vancomycin nonsusceptible enterococci; (3) penicillin-resistant and/or ceftriaxone nonsusceptible *Streptococcus pneumoniae*; (4) third-generation cephalosporin (eg, ceftriaxone)-nonsusceptible *Enterobacteriaceae* and isolates expressing various β-lactamases including extended-spectrum beta-lactamases (ESBLs), bla_{AmpC}, and various carbapenemases (eg, bla_{KPC}), as previously described; (5) *Pseudomonas aeruginosa*; (6) *Acinetobacter baumannii*; and (7) *Stenotrophomonas maltophilia* [25].

Definitions

Invasive devices were defined as any of the following devices in situ for at least 48 hours in the 3 months before BSI; tracheotomy, permanent pacemaker, central venous catheter, urinary catheter, external orthopedic fixation device, gastrostomy, or other percutaneous drain tube. Internal stents, prosthetic heart valves, and prosthetic joints were excluded.

Invasive procedures were defined as any of the following performed in the 3 months before BSI; surgical procedure (including biopsy), endoscopy, long-term vascular device insertion,

urinary catheter insertion, and any percutaneous interventions including cardiac catheterization and feeding tube insertion.

Neurologic disease was defined as the presence of a chronic neurologic condition of idiopathic, autoimmune, degenerative, or vascular etiology.

Immunosuppression was defined as the presence of any of the following conditions at the time of positive blood culture: neutropenia (neutrophil count < 0.5), corticosteroid therapy (≥2 consecutive days or 5 days overall in the past month), receipt of chemotherapy or radiotherapy in the previous 3 months, receipt of immunomodulatory agents (eg, tumor necrosis factor–alpha inhibitors) in previous 3 months, HIV infection, and bone marrow or solid organ transplantation.

Data Collection

Clinical data were retrieved from all available hospital records and databases. Mortality data were retrieved from the Israeli Ministry of Interior. Data collected included: demographics, possible health care exposures, comorbidities and underlying conditions, acute illness indices, microbiological data, and clinical outcomes. Two experienced infectious diseases specialists determined the likely source of BSI. For the development of the new score, only parameters that were clearly defined and could be measured in a reproducible way were chosen.

Statistical Analyses

All analyses were performed in Stata 13.1 (Stata Corp, College Station, TX). Among the patients with community-onset BSI, all potential predictors were entered into an MDRO risk factors model (logistic regression), and a first model was derived using backwards elimination [26]. The model with the lowest Akaike Information Criteria (AIC) value was selected. We assessed the model's performance by a calibration plot, the Hosmer-Lemeshow goodness-of-fit test, and by calculating the area under the receiver operating characteristic (ROC) curve (AUC). Because parsimony makes prediction models easier for clinicians to use, we used the roccomp command in Stata to test whether covariates could be omitted without significantly decreasing the AUC. Interactions between covariates were also tested. The internal validity of the model was assessed by bootstrapping on 200 samples. To create the scoring system, points were assigned to each covariate by multiplying the coefficient by 2 and rounding to the nearest integer.

We compared the AUC of the score model with that of the multivariable model to assess to what degree the rounding was necessary to create a scoring system that affected predictive performance [27]. Next, for each possible cut-point, we calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the proportion of patients who were classified as high risk. We chose as our cut-point the score that maximized Youden's index. Finally, we assessed the predictive performance of the Duke-2002 [15], modified Duke-2002 [16], and Pitt bacteremia score (≥4 points) [28] at predicting MDRO-BSI on admission (primary aim) and for in-hospital mortality (secondary aim).

RESULTS

Patient Characteristics

Five hundred four patients were included in the final study cohort: 315 had a BSI present on admission (100 with MDRO-BSI and 215 with non-MDRO-BSI), and 189 patients had a nosocomial BSI. The majority of the study population was elderly with both extensive health care exposure and markers of severe acute illness. Nearly half had at least severe sepsis, per established criteria [23], and over one-third had a rapidly fatal McCabe score (indicating survival <1 year) [29]. The most common source of BSI was urinary tract infection (40%), followed by respiratory tract infection (19%), whereas primary bacteremias comprised only 5% (Table 1).

Univariable Comparisons Between Patient Groups

Patients with an MDRO-BSI on admission (n = 100) resembled patients with nosocomial BSI (n = 189) much more than they resembled patients with non-MBDO-BSI on admission (n = 215).

These similarities included recent prior health care exposure, rates of residency in an LTCF, background medical conditions, acuity levels of sepsis [23], and clinical outcomes (data not shown).

The delay before receipt of appropriate antimicrobials was significantly longer in patients with nosocomial BSI or MDRO-BSI on admission, compared with patients with a non-MDRO-BSI on admission (P = .02 between groups). In-hospital mortality rates were higher (P < .001), and length of hospital stay longer (P < .001), among patients with either nosocomial or MDRO-BSI on admission, compared with patients with non-MBDO-BSI on admission.

Comparing the 100 patients with MBDO-BSI on admission (cases) and the 215 patients with non-MBDO-BSI on admission (controls), cases were more likely to be male, of older age, with more health care exposure, with higher comorbid illness scores and deteriorated clinical status in their background. Moreover, cases had increased illness acuity, greater delay in initiation of appropriate therapy, and worse outcomes (Table 1).

Microbiology

The leading causative pathogen of BSI was *E. coli* (n = 129, 24%), followed by *S. aureus* (n = 67, 12%) and *K. pneumoniae* (n = 53, 10%). Seventeen BSIs were polymicrobial. And the majority of BSIs (68%) were caused by aerobic Gram-negative bacteria (Table 2).

MDROs included ESBL producers (91), MRSA (32), ampicillin-resistant enterococci (16), and penicillin-nonsusceptible *S. pneumoniae* (1).

Table 1. Epidemiological Characteristics of Study Patients With Bloodstream Infection on Admission to an Acute Care Hospital

Parameter	MDRO on Admission		OR (95% CI)	*P* Value
	Yes (n = 100), No. (%)	No (n = 215), No. (%)		
Demographic characteristics				
Male sex	52 (52)	79 (36.7)	1.9 (1.2–3.0)	.01
Age ≥70 y	78 (78)	122 (56.7)	2.7 (1.6–4.7)	<.001
Exposure to health care				
Hospitalization in previous 90 d	66 (66)	83/214 (38.8)	3.1 (1.9–5.0)	<.001
Residence in LTCF before hospitalization	50 (50)	28 (13.0)	6.7 (3.8–11.7)	<.001
Regular (at least weekly) outpatient visits	12 (12)	39/214 (18.2)	0.61 (0.31–1.2)	.17
Hemodialysis	8 (8)	4 (1.9)	4.6 (1.3–15.6)	.02
Home IV or wound care in previous 30 d	11 (11)	7 (3.3)	3.7 (1.4–9.8)	.01
Antibiotic use in previous 90 d	56/99 (56.6)	54 (25.1)	3.9 (2.3–6.4)	<.001
Invasive procedure in previous 3 mo	53 (53)	67 (31.2)	2.5 (1.5–4.1)	<.001
Invasive device present on admission	42 (42.4)	46/214 (21.5)	2.7 (1.6–4.5)	<.001
Underlying conditions				
Poor functional status [39]	81 (81)	102/214 (47.7)	4.7 (2.7–8.3)	<.001
Ischemic heart disease	15 (15)	30 (14)	1.1 (0.56–2.1)	.81
Congestive heart failure	22 (22)	30 (14)	1.7 (0.94–3.2)	.08
Diabetes	50 (50)	93 (43.3)	1.3 (0.82–2.1)	.26
Chronic renal disease (including hemodialysis patients)	38 (38)	39 (18.1)	2.8 (1.6–4.7)	<.001
Chronic lung disease	20 (20)	31 (14.4)	1.5 (0.80–2.8)	.21
Neurological disease	55 (55)	61 (28.4)	3.1 (1.9–5.1)	<.001
Impaired cognition (including dementia)	55 (55)	57 (26.5)	3.4 (2.1–5.6)	<.001
Active malignancy	21 (21)	62 (28.8)	0.66 (0.37–1.2)	.14
Chronic skin ulcers	41 (41)	43 (20)	2.8 (1.7–4.7)	<.001
Immunosuppression	37 (37)	53 (24.7)	1.8 (1.1–3.0)	.03
Source of bacteremia				
Urinary tract infection	33 (33)	101 (46.9)	0.6 (0.4–1)	.04
Pneumonia	26 (26)	35 (16.3)	1.9 (1.1–3.3)	.03
Skin and soft tissue infection	21 (21)	31 (14.4)	1.6 (0.9–2.9)	.14
Intrabdominal infection	14 (14)	30 (13.9)	1 (0.5–2)	.9
Primary bloodstream infection	4 (4)	11 (5.1)	0.8 (0.3–2.6)	.72
Endocarditis	4 (4)	11 (5.1)	0.8 (0.2–2.5)	.7
Acute illness indices				
Severe sepsis, septic shock, multi-organ failure [23]	59 (59)	63 (29.3)	3.5 (2.1–5.7)	<.001
McCabe score, mean ± SD [29]	2 ± 1	2 ± 1		<.001
Pitt bacteremia score [28], median (IQR)	2 (0–14)	0 (0–1)		<.001
Clinical outcomes				
Days to appropriate therapy, median (IQR)	2 (0–9)	0 (0–7)		<.001
Death during current hospitalization	45 (52.9)	40 (18.6)	3.7 (2.2–6.3)	<.001
Death within 30 d of culture date	45 (45)	45 (20.9)	3.2 (1.9–5.4)	<.001
Death within 90 d of culture date	57 (46.7)	65 (30.2)	3.2 (2–5.2)	<.001
Length of stay (excluding deceased patients), median (IQR), d	11 (0–35)	7 (1–100)		<.001

Abbreviations: CI, confidence interval; IQR, interquartile range; LTCF, long-term care facility; MDRO, multidrug-resistant organism; OR, odds ratio; SIRS, systemic inflammatory response syndrome.

Multivariable Analysis of Risk Factors for MDRO on Admission

This analysis was undertaken on 315 hospitalizations (100 MDRO and 215 non-MBDO-BSIs) among 296 unique patients. Three subjects with missing values for any covariate were excluded, resulting in a sample size of 312. Based on the results of the univariate analysis, 7 variables were included in the logistic regression analysis.

The model included 6 risk factors (hospitalization in the past 90 days, LTCF stay before hospitalization, dialysis, antibiotic use in the past 90 days, neurological disease, and severe sepsis) and 1 protective factor (regular outpatient visits) (Table 3). The *P* value for the Hosmer-Lemeshow test was .47, indicating agreement between observed and predicted probabilities. The AUC was 0.81 (95% confidence interval [CI], 0.76–0.85). Internal validation of the model using bootstrapping yielded an optimism-adjusted AUC of 0.79.

MDRO Infection on Admission Score

Table 3 shows the MDRO on admission model with coefficients and the points assigned to devise the scoring system.

Table 2. Microbiological Isolates

		Frequency, No.	%
Aerobic Gram-positive isolates		173	32
Species	Bacteria		
Aerobic Gram-positive	*Staphylococcus aureus*	67	12.3
	Enterococcus faecalis	42	7.7
	Streptococcus viridans group	14	2.6
	Streptococcus pneumoniae	13	2.4
	Enterococcus faecium	11	2.0
	Group B streptococcus	7	1.3
	Group A streptococcus	6	1.1
	Enterococcus spp.	4	0.7
	Group D streptococcus	3	0.6
	Listeria monocytogenes	3	0.6
	Group C and G streptococcus	2	0.4
	Leuconostoc spp.	1	0.2
Aerobic Gram-negative isolates		371	68
Aerobic Gram-negative	*Escherichia coli*	129	23.7
	Klebsiella pneumonia	53	9.7
	Pseudomonas aeruginosa	46	8.5
	Acinetobacter baumannii	29	5.3
	Proteus mirabilis	28	5.1
	Providencia stuartii	14	2.6
	Morganella morganii spp. *morganii*	11	2.0
	Enterobacter cloacae	10	1.8
	Acinetobacter spp.	9	1.7
	Serratia marcescens	6	1.1
	Pseudomomnas spp.	6	1.1
	Klebsiella oxytoca	5	0.9
	Haemophilus influenzae	4	0.7
	Enterobacter spp.	4	0.7
	Neisseria spp.	3	0.6
	Salmonella spp.	2	0.4
	Citrobacter koseri	2	0.4
	Escherichia hermannii	1	0.2
	Branhamella catarrhalis	1	0.2
	Citrobacter freundii	1	0.2
	Serratia liquefaciens group	1	0.2
	Achromobacter xylosoxidans	1	0.2
	Aeromonas sobria	1	0.2
	Eikenella corrodens	1	0.2
	Myroides spp.	1	0.2
	Raoultella planticola	1	0.2
	Stenotrophomonas maltophilia	1	0.2
Total bacterial isolates		544	100

Possible scores range from –2 to 12. The observed scores in our sample ranged from –2 to 8. Table 4 summarizes the performance of the scoring system at different cut-points. Based on Youden's index, 3 was chosen as the cut-point (ie, scores ≥3 indicate a high risk of an MDRO infection). At this level, 43% of patients were classified as high risk, sensitivity was 79%, and specificity was 73%. PPV was 58%, and NPV was 88%. Using this cut-point, the AUC was 0.76 (95% CI, 0.71–0.81) (Table 5).

The initial model was repeated, omitting the protective variable of regular outpatient visits, to create a new scoring system based on the coefficients. Results were similar to the original model: using the cut-point with the highest Youden's index, the AUC was 0.74 (95% CI, 0.69–0.79).

Performance of the Model in Comparison With Previous Definitions of HcAI

Using both the Duke-2002 definition and the modified Duke-2002 definition to predict BSI caused by an MDRO on admission

Table 3. Final Multivariable Model and Prediction Score for MDRO-BSI on Admission

Parameter	β-Coefficient	Odds Ratio (95% CI)	*P* Value	Points
Hospitalization in previous 90 d	0.51	1.7 (0.87–3.2)	.13	1
Residence in LTCF before hospitalization	1.5	4.3 (2.2–8.3)	<.001	3
Regular (weekly) outpatient visits	–1.0	0.36 (0.14–0.94)	.04	–2
Hemodialysis	2.1	8.0 (1.7–36.9)	.01	4
Antibiotic use in previous 90 d	0.84	2.3 (1.2–4.4)	.01	2
Neurological disease	0.51	1.7 (0.9–3.1)	.10	1
Severe sepsis or septic shock[a]	0.48	1.6 (0.90–2.9)	.10	1

Abbreviations: BSI, bloodstream infection; CI, confidence interval; LTCF, long-term care facility; MDRO-BSI, multidrug-resistant organism bloodstream infection.

[a]Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion; septic shock is defined as severe sepsis plus hypotension not reversed with fluid resuscitation [23].

in our cohort, results were very similar, with negative predictive values of approximately 90%, but poor accuracy at predicting MDRO-BSI on admission based on AUC scores <0.7 (Table 5). Using the Pitt bacteremia score of ≥4 to predict BSI caused by an MDRO on admission, specificity was high but sensitivity was extremely poor, and the AUC was 0.59 (Table 5).

The Duke-2002 and the modified Duke-2002 definitions performed poorly at predicting in-hospital mortality among this cohort, with AUC scores of 0.67 and 0.63, respectively. The Pitt bacteremia score ≥4 performed modestly at predicting in-hospital mortality, with an AUC of 0.7.

DISCUSSION

The contemporary structure of health care with increasing health care delivery outside of acute hospitals has created a population of patients who may develop infections with their onset in the community, but who need to be distinguished from those with traditional community-acquired infections. In terms of patient characteristics and outcomes, HcAIs resemble nosocomial infections more than they resemble CA infections. This has been clearly shown both in this cohort and in the original Duke-2002 study [15].

The important similarities between patients with nosocomial and HcAIs include demographic characteristics (sex and age), severity of comorbidity and acute illness indices, and the types and frequency of causative pathogens (ie, the prevalence of MDROs). Moreover, the rates of worse clinical outcomes are relatively similar among these groups and are usually significantly worse than among those with traditional CA infections [15, 30].

The initial and most accepted definition of HcAI and variations thereof have been widely used both in the literature and in clinical practice [15, 16]. Professional societies have used the Duke-2002 HcAI definition, or slight modifications of it, predominantly to guide clinicians on when to suspect an infection caused by an MDRO and act accordingly [18]. However, the Duke-2002 definition was developed a priori by the authors before study initiation [15]. Although this initial definition proved the overall similarities of patients with HcAI and patients with nosocomial infections, it was neither developed nor validated to predict MDRO infection on admission [15]. Moreover, these definitions falsely assume a homogeneity of the heterogeneous HcA patient group, thereby guiding broad-spectrum treatment decisions that may have adverse consequences both individually and ecologically [20].

In this analysis of 504 patients with BSI over a 7-month period in a university-affiliated, acute care hospital, we attempted to develop a definition for HcAI based on its ability to predict an

Table 4. Predictive Performances of the MDRO-BSI on Admission Prediction Score at Different Cutoffs

Cut-Point	Patients Classified as High Risk, %	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
≥–2	100	100	0	32	–
≥–1	97	99	4	32	89
≥0	93	97	8	33	86
≥1	71	92	39	41	91
≥2	53	85	62	51	90
≥3	43	79	73	58	88
≥4	35	70	82	64	85
≥5	26	55	88	68	81
≥6	17	40	94	75	77
≥7	11	23	95	70	73
≥8	5	11	98	73	70

Abbreviation: MDRO-BSI, multidrug-resistant organism bloodstream infection.

Table 5. Performance of Previously Used Definitions at Predicting MDRO-BSI on Admission

Definition/Score	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %	Area Under the ROC Curve
MDRO infection on admission	79	73	58	88	0.76
Duke-2002	87	49	44	89	0.68
Modified Duke-2002	90	43	42	90	0.66
Pitt's bacteremia score ≥4	27	92	60	73	0.59

Abbreviations: MDRO-BSI, multidrug-resistant organism bloodstream infection; ROC, receiver operating characteristic.

MDRO infection of community onset. We demonstrated that community-onset MDRO infections (ie, HcAIs) resemble nosocomial infections more than they resemble community-onset non-MDRO infections (CA infections) and that previously identified risk factors for HcAI—hospitalization, hemodialysis, antibiotic use, and residence in an LTCF—also predict an MDRO-BSI on admission.

It is unclear why our analysis identified neurological disease as a risk factor for MDRO-BSI; we suspect that neurological disease may be a surrogate marker for other factors such as recent hospitalization and debilitated status. Similarly, it is uncertain why outpatient visits were protective against BSI caused by an MDRO on admission to the hospital, as this variable was not protective in Duke-2002 [15].

However, we acknowledge the only fair performance of our definition for discriminating the population at risk for an MDRO infection on admission. The ROC AUC was only 0.74, the sensitivity and specificity were both below 80%, and if this score were applied, 40% of the patients with an MDRO infection on admission would still be adversely affected by a delay in initiation of appropriate antimicrobial therapy. Moreover, 12% of patients with a non-MDRO infection would receive unnecessary broad-spectrum (and sometimes toxic) antibiotics, which are harmful both in terms of the individual patient [31] and in terms of the ecological impact within a facility [32]. When the Duke-2002 and modified Duke-2002 definitions were applied to this cohort, the discriminating power was poor at predicting an MDRO infection on admission, with ROC AUC scores of only 0.68 and 0.66, respectively. The performance of a positive Pitt bacteremia score was similarly unsatisfactory. Improving the ability to predict infection caused by an MDRO will require further study on larger patient cohorts.

This study has several limitations. Inaccurate or missing data may have resulted in information bias given the retrospective nature of data collection. Although we included all known important confounders relevant for antimicrobial resistance studies, there may have been other unmeasured confounding factors. In addition, some variables in this study, such as previous procedures or immunosuppression, could not be stratified to determine more precisely the relative risk of infection acquisition.

We also acknowledge the possibility of misclassification bias if patients with blood cultures yielding a contaminant were included. However, as we included only cases determined to be BSIs, we believe this to be unlikely. Moreover, this study focused only on BSIs, both primary and secondary, eliminating other infectious syndromes without BSI. Patients in this study with neurologic disease may have functional disability (poor functional status), and therefore it is acknowledged that this group could act as a confounder in the multivariable analysis. It is also unclear if our results are generalizable to other facilities in other countries, where the incidence of MDROs among outpatients is different. Finally, the authors acknowledge that our sample population was used to develop the new risk score, and therefore there was no validation cohort in this study.

An established and validated HcAI definition to guide both daily clinical practice and infection surveillance is needed. Moreover, HcAI needs agreed-upon and uniform nomenclature to avoid potentially confusing terminology, such as "community onset," "community associated," "outpatient infections," "infections among nonhospitalized patients," "non-nosocomial," and "infections in first 48 hours of hospitalization" [33–38].

In conclusion, this study demonstrates that HcAI definitions based on the original Duke-2002 definition, the modified Duke-2002, the Pitt bacteremia score, or the score-based definition developed in this study perform poorly at predicting infection caused by an MDRO on hospital admission. Despite these shortcomings, the similarities between HcAI and nosocomial infections are clear, and MDROs are indeed significantly more prevalent among patients with health care exposure. Clinicians and professionals creating therapeutic guidelines should recognize these similarities yet exercise caution when utilizing an HcAI definition with suboptimal performance to guide therapeutic recommendations.

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