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High Burden of Antimicrobial Resistance and Mortality Among Adults and Children With Community-Onset Bacterial Infections in India

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Background. In India, antimicrobial consumption is high, yet systematically collected data on the epidemiology, risk factors, and outcomes of antimicrobial-resistant infections are limited.

Methods. A prospective study of adults and children hospitalized for acute febrile illness was conducted between August 2013 and December 2015. In-hospital outcomes were recorded, and logistic regression was performed to identify independent predictors of community-onset antimicrobial-resistant infections.

Results. Among 1524 patients hospitalized with acute febrile illness, 133 isolates were found among 115 patients with community-onset infections; 66 isolates (50.0%) were multidrug resistant and, of 33 isolates tested for carbapenem susceptibility, 12 (36%) were resistant. Multidrug-resistant infections were associated with recent antecedent antibiotic use (adjusted odds ratio [aOR], 4.17; 95% confidence interval [CI], 1.19–19.7) and were independently associated with mortality (aOR, 6.06; 95% CI, 1.2–55.7).

Conclusion. We found a high burden of community-onset antimicrobial-resistant infection among patients with acute febrile illness in India. Multidrug-resistant infection was associated with prior antibiotic use and an increased risk of mortality.

Keywords. antimicrobial resistance; community onset; clinical isolates; India.

The emergence of antimicrobial resistance has become a global crisis. Contributing factors include unregulated access to antimicrobials, clinical overuse, inadequate diagnosis, agricultural antimicrobial use, and ineffective infection control [1–3]. Management of life-threatening, drug-resistant bacterial infections is challenging. Therapeutic options are limited, often require parenteral administration, are costlier, and have more adverse effects. Drug-resistant infections also incur increased hospitalization costs, length of stay, and mortality. These issues are magnified in low-income and middle-income settings.

With a population of 1.2 billion, India is among the countries with greatest global bacterial disease burden [1]. Antimicrobial use is common in India and has increased dramatically over the past 20 years [3]. However, systematically collected data on antimicrobial resistance are limited in both inpatient and community settings. Knowledge of antimicrobial resistance patterns and the availability of appropriate antimicrobials are essential to prevent the substantial morbidity and mortality associated with drug-resistant infections.

Most studies to date have focused on single organisms or outbreaks rather than on broader evaluation of the epidemiology of bacterial infections [2, 4–7]. In 2009–2010, there was a worldwide emergence of an organism containing multiple resistance determinants, coined "New Delhi metallo-β-lactamases," that in part originated from a tertiary care hospital in New Delhi [8]. The emergence of New Delhi metallo-β-lactamases highlighted the antimicrobial resistance problem in India, demonstrated how rapidly an organism can spread throughout the world, and highlighted the lack of systematically collected antimicrobial resistance data in India and most low-income and middle-income countries. While organisms expressing New Delhi metallo-β-lactamases may be the most well-known example of multidrug-resistant (MDR) gram-negative organisms in India, numerous studies have long documented the rising rates of resistance to commonly used antimicrobials, as well as extended-spectrum β-lactamases, among gram-negative organisms [9, 10]. However, little is known about antimicrobial resistance in community-onset febrile illness.

Understanding antimicrobial resistance in India may serve several purposes [2], including generating evidence to support advocacy for the regulation of currently unregulated antibiotic prescription; to develop evidence-based treatment guidelines; to guide policy for antibiotic stewardship programs, which are

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presently nonexistent in most settings; and to emphasize the need for universal, standardized infection control guidelines. We aimed to describe the burden, risk factors, and outcomes of community-onset bacterial infection among adults and children admitted with acute febrile illness (AFI) to a large, public tertiary care facility in western India.

METHODS

Study Design

We conducted a study of adults and children admitted to Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospitals (BJGMC-SGH) with AFI between July 2013 and December 2015. BJGMC-SGH is a 1400-bed tertiary care public teaching hospital in Pune, Maharashtra, serving a population of approximately 7 million in urban, semiurban, and rural areas. Eligible participants ages >6 months were identified from admission logbooks in inpatient medicine and pediatric wards, which were reviewed on working days for history of AFI. Patients with a self-reported or documented temperature of ≥38°C for a duration of ≥24 hours were approached for enrollment. Patients transferred directly from another healthcare facility to BJGMC-SGH or those reporting hospitalization or surgery in the 3 months before admission were excluded.

Informed consent was obtained from eligible adult patients and from the legal guardian of eligible children aged <18 years; assent was obtained for children aged >12 years. This study was approved by the BJGMC-SGH Ethics Committee and the Institutional Review Board of Johns Hopkins University School of Medicine.

Assessments

A dedicated study physician and social worker recorded each participant's clinical history by means of a standardized method, and provisional admission diagnoses made by the hospital clinical team were recorded. Treating clinicians used a case record form to record clinical features at admission and discharge, as well as the results of routine laboratory investigations. On admission, the study team collected blood from all participants as per study protocol. Participants' skin was cleansed, and a 5-mL blood sample was collected for aerobic and anaerobic blood culture. Additional specimens were collected to determine AFI etiology. All participants with unknown human immunodeficiency virus (HIV) status were offered and consented to undergo rapid HIV testing. In addition to systematically collection blood specimens at admission for culture, the study team used medical and laboratory records to abstract all additional bacterial culture results for any type of specimen as part of routine care until discharge.

Laboratory Procedures

Bactec standard aerobic bottles were loaded into the Bactec Microbial Detection system (Becton Dickinson) and incubated for 5 days. Standard methods were used to identify bloodstream isolates, which included subculture in blood and MacConkey agar. Bacterial species identification and antimicrobial susceptibility testing were performed according to Clinical Laboratory Standards Institute (Wayne, PA) guidelines, using the Phoenix Automated Microbiology System (Becton Dickinson) [11]. For cultures other than those of blood samples, specimens were directly plated onto blood and MacConkey agar and underwent manual identification of bacterial species and testing for drug susceptibility. During the study, the laboratory had positive results of relevant external quality assurance assessments by the College of American Pathologists and the Viral Quality Assurance program of the AIDS Clinical Trials Group.

Study Outcomes and Definitions

Primary outcomes were culture-positive community-onset infection and detection of MDR pathogens. Isolates identified as coagulase-negative *Staphylococcus* species, *Micrococcus* species, *Dermacoccus* species, *Bacillus* species, and other environmental flora were considered to be contaminants and excluded from analysis. Additionally, enterococcus isolated in urine culture was considered to be a contaminant. Community-onset and hospital-onset infections were defined by the presence of positive clinical cultures obtained ≤2 and >2 days after admission, respectively, according to the Centers for Disease Control and Prevention surveillance definitions [12, 13]. Pathogenic isolates were classified as MDR according to consensus definitions from the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention [11]. MDR was defined as nonsusceptibility to at least 1 agent in at least 3 antimicrobial categories specific to the following groupings: *Staphylococcus aureus*, *Enterococcus* species, Enterobacteriaceae other than *Shigella* and *Salmonella*, *Pseudomonas* species, and *Acinetobacter* species. As consensus definitions did not include *Salmonella*, *Shigella*, and *Streptococcus* species, existing definitions from other sources were used. *Salmonella* isolates resistant to ≥2 of the following antimicrobials were classified as MDR: amoxicillin, trimethoprim-sulfamethoxazole, chloramphenicol, or tetracyclines. *Shigella* isolates resistant to ≥3 classes of antimicrobials were classified as MDR. *Streptococcus pneumoniae* isolates not susceptible to penicillin and at least 2 other non–β-lactam antimicrobial classes were classified as MDR [14]. Carbapenem-resistant gram-negative rods (GNRs) with insufficient data to otherwise meet the above guidelines were also considered to be MDR. Secondary outcomes included length of hospitalization and in-hospital all-cause mortality. Severe malnutrition among children was defined as a weight-for-height score <3 standard deviations below the median, using the World Health Organization growth charts for children aged <5 years and the Indian Academy of Pediatrics growth charts for children ages 5–12 years [15].

Analyses

Data were entered into Microsoft Access software. Baseline categorical and continuous variables are summarized using proportions and medians with interquartile ranges (IQRs), respectively, and compared using the Fisher exact test or Wilcoxon rank sum test as appropriate; *P* values of <.05 were deemed statistically significant. To evaluate predictors for MDR organisms, we assessed selected clinical and demographic variables, using univariate regression and multivariate logistic regression analysis. Multivariate models were fitted to estimate the odds ratio (OR) that adjusted for covariates with *P* values of <.1 in univariate analysis, covariates known to be associated with a risk of infection with MDR organisms, and demographic variables. A multivariable model was created to evaluate the association of community-onset infection with MDR organisms, with adjustment for demographic variables and the type of infection. All statistical analyses were performed using R software (version 3.2.1; available at: http://www.cran.r-project.org).

RESULTS

Participant Characteristics

Of 57 177 patients admitted to BJGMC-SGH medicine and pediatric wards during the study period, 6339 with admission logbook diagnoses suggestive of AFI were screened. Of these 6339 patients, 3161 met criteria for AFI, and 1524 met study-specific inclusion criteria. Reasons for noninclusion are shown in Figure 1. The study population comprised 842 adults and adolescents (ie, individuals aged ≥12 years; median age, 29 years [IQR, 21–45 years]) and 682 children ages 6 months through 11 years (median age, 2 years [IQR, 1–6 years]). Overall, 58% were male, 52% received intravenous antibiotics before a blood specimen was obtained for culture, and 12% of adults and 1% of children had documented or reported HIV infection (Table 1). Patients who received in-hospital antibiotics prior to collection of blood specimens for culture were more likely to be adults (*P* < .01) and less likely to be admitted to the ICU (*P* = .01).

Any Bacterial Infection

Of 1524 participants admitted with AFI, blood specimens were collected from 1506 patients at admission for culture, of whom 203 had positive culture results, including 148 with contaminants and 59 (4%) with noncontaminant organisms. Cultures for 1 patient grew 2 pathogenic organisms. An additional 69 patients had community-onset infections with positive results of cultures involving specimens from other sites, including 27 cultures of urine specimens, 15 cultures of respiratory specimens, 14 cultures of CSF specimens, and 17 cultures of specimens from other sources; 4 patients had 2 isolates detected on culture. Thus, 133 pathogenic isolates were obtained from

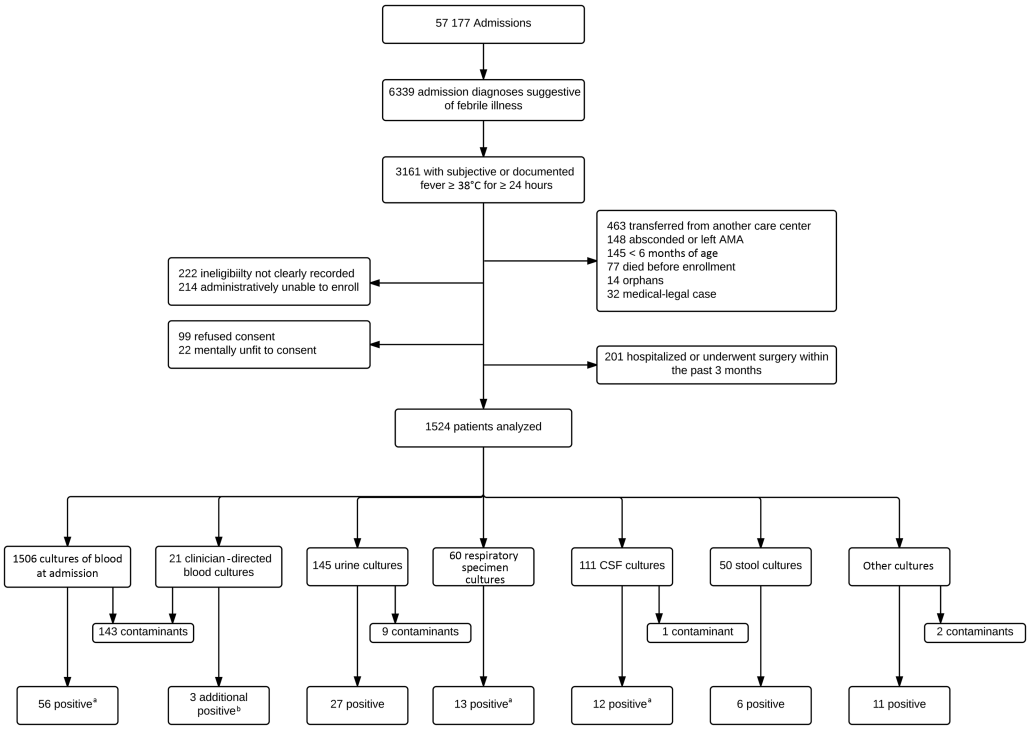

Figure 1. Flow diagram of study enrollments and collection of cultures among adults and children hospitalized for acute febrile illness (AFI) in Pune, India. AMA, against medical advice; CSF, cerebrospinal fluid. [a]One blood culture, 2 respiratory specimen cultures, and 2 CSF cultures grew 2 organisms. [b]Results of 4 cultures were positive; 1 positive result was already identified by culture of a blood specimen obtained at admission.

Table 1. Characteristics of Adults and Children Hospitalized With Acute Febrile Illness, by Isolation of a Bacterial Pathogen From Any Clinical Culture

Characteristic	Overall (n = 1524)	Pathogen Isolated			Adults (n = 842), Pathogen Isolated			Children (n = 682), Pathogen Isolated		
		No (n = 1409)	Yes (n = 115)	*P*	No (n = 777)	Yes (n = 65)	*P*	No (n = 632)	Yes (n = 50)	*P*
Age, y	17 (3–31)	17 (3–30)	21 (3–43.5)	.06	28 (21–43)	40 (30–56)	<.01	2 (1–6)	2 (1–6)	.52
Male sex	882 (58)	823 (58)	59 (51)	.14	466 (60)	36 (55)	.51	357 (56)	23 (46)	.18
Alcohol use (adults only)[a]	…	…	…		66 (10)	10 (24)	.02	…	…	
Smoking (adults only)[a]	…	…	…		81 (13)	3 (7)	.46	…	…	
Income <5000 rupees/mo	605 (40)	538 (38)	67 (58)	<.01	281 (36)	38 (58)	<.01	257 (41)	29 (58)	.02
Blood cultures performed before antibiotic use[b]	712 (48)	658 (48)	54 (48)	1	278 (37)	21 (34)	.68	380 (62)	33 (66)	.65
Diabetes mellitus[a]	42 (3)	36 (3)	6 (9)	.03	35 (5)	6 (14)	.03	1 (0)	0 (0)	1
HIV positive[c]	109 (13)	95 (13)	14 (19)	.1	83 (12)	13 (23)	.04	12 (18)	1 (7)	.44
Severe malnutrition (children only)	…	…	…		…	…		116 (21)	4 (9)	.05
Antibiotic use within past mo	357 (23)	332 (24)	25 (22)	.73	203 (26)	17 (26)	1	129 (20)	8 (16)	.58
Antibiotic use within past wk	324 (21)	302 (21)	22 (19)	.64	187 (24)	16 (25)	.88	115 (18)	6 (12)	.34
Length of stay, d	4 (3–7)	4 (3–7)	5 (3–12)	<.01	3 (2–5)	4 (3–7.25)	<.01	6 (4–10)	6.5 (4–13.8)	.23
In-hospital mortality	119 (8)	101 (7)	18 (16)	<.01	53 (7)	10 (16)	.02	48 (8)	8 (17)	.05

Data are median (interquartile range) or no. (%) of participants. Adults and adolescents are defined as participants aged ≥12 years. Children are defined as participants aged 6 months to 12 years. Nonpathogenic isolates have been excluded.

[a]Data for alcoholism, smoking, and diabetes were not collected for the first 5 months of the study. Percentages reflect a denominator of 688 adults and 545 children.

[b]Information was not available for 41 patients.

[c]Human immunodeficiency virus (HIV) status was known for 746 adults; data were not systematically collected for all children.

115 patients (Table 2 and Supplementary Table 1), comprising 97 patients with monomicrobial infections, 15 patients with polymicrobial infections, and 3 patients with the same organism recovered from 2 different specimen sources. Patients with culture-positive community-onset infections represented 7% of the study population, which comprised 65 adults/adolescents (8%) and 50 children (7%). Patients with a culture-positive community-onset bacterial infection were more likely to report lower income ($P < .01$) and diabetes mellitus ($P = .03$) than those with culture-negative AFI (Table 1). Among adults and adolescents, those with a culture-positive bacterial infection were older (median age, 40 years [IQR, 30–56 years] vs 28 years [IQR, 21–43 years]; $P < .01$), more likely to report alcohol abuse ($P = .02$), have lower income ($P < .01$), have a longer hospitalization duration ($P < .01$), and have higher in-hospital mortality ($P = .02$) than those with culture-negative AFI (Table 1). Among children, we observed lower household income ($P = .02$) and higher in-hospital mortality ($P = .05$) in those with culture-positive community-onset bacterial infection.

Of 133 bacterial pathogenic isolates from patients with community-onset infections, 102 (77%) were GNR, primarily composed of Enterobacteriaceae (n = 57; predominantly *Escherichia coli* [31 {23%}], *Klebsiella* [11 {8%}], *Acinetobacter* (18 {13%}], and *Pseudomonas* [12 {9%}]); 31 pathogenic isolates were gram-positive organisms, primarily *S. aureus* (12 [9%]), *Enterococcus* (6 [4%]), and *Streptococcus* species 6 (4%; Table 2). *E. coli* was the predominant species in urinary tract (12 [44.4%]) and respiratory (3 [20%]) specimens.

Among 1524 enrolled patients, 140 isolates were recovered from 105 with hospital-onset infections. The species of hospital-onset bacterial isolates, by specimen source and antimicrobial-susceptibility patterns, are described in Table 3 and Supplementary Table 2. Interestingly, there were similar species and high MDR prevalence noted among GNR isolated from patients with hospital-onset or community-onset infections. The species breakdown of the 155 contaminant isolates obtained from 148 participants was as follows: 64 were coagulase-negative *Staphylococcus* species, 31 were *Micrococcus* or *Dermacoccus* species, 14 were *Bacillus* species, 8 were *Enterococcus* from urine specimens, and 43 were other species (Supplementary Table 3). Among the 155 contaminant cultures, 143 were derived from blood. Hereafter we focus on community-onset infections.

Bloodstream Infections

Of 115 patients with community-onset culture-positive bacterial infections, 59 (51%) had 60 confirmed bloodstream pathogens. The most common pathogenic isolates were *Acinetobacter* species (13 [21.7%]), followed by *E. coli* (9 [15%]; Table 2). We noted that blood culture positivity was similar among patients who did and those who did not receive antibiotics prior to collection of blood specimens for culture ($P = .50$).

Community-Onset MDR Bacterial Infection (Table 4)

The majority of community-onset bacterial infections, involving 60 of 115 patients (52%) and 66 of 133 isolates (50%), were due to MDR organisms (Figure 2). Overall, the vast majority of

Table 2. Species of Community-Onset Pathogenic Bacterial Isolates Recovered on Culture Among 115 Patients, by Clinical Specimen Cultured

Organism	Overall (n = 133)	Blood, Collected Before Antibiotic Treatment (n = 25)	Blood, Collected After Antibiotic Treatment (n = 35)	CSF (n = 14)[a]	Urine (n = 27)	Respiratory (n = 15)[b]	Other (n = 17)
Gram-negative rods							
Escherichia coli	31 (23)	…	9 (26)	2 (14)	12 (44)	3 (20)	5 (29)
Acinetobacter species	18 (13)	7 (28)	6 (18)	2 (14)	2 (7)	1 (7)	…
Pseudomonas species	12 (9)	1 (4)	…	3 (21)	3 (11)	2 (13)	3 (18)
Klebsiella species	11 (8)	1 (4)	2 (6)	2 (14)	4 (15)	1 (7)	1 (6)
Enterobacter	7 (5)	…	…	1 (7)	3 (11)	2 (13)	1 (6)
Unspecified	5 (4)	…	1 (3)	1 (7)	1 (4)	2 (13)	…
Burkholderia cepacia	4 (3)	…	4 (12)	…	…	…	…
Citrobacter	4 (3)	…	…	…	2 (7)	2 (13)	…
Salmonella species	2 (2)	2 (8)	…	…	…	…	…
Sphingomonas paucimobilis	3 (2)	3 (12)	…	…	…	…	…
Shigella flexneri	2 (1)	1 (4)	…	…	…	…	1 (6)
Pasteurella aerogenes	1 (1)	…	1 (3)	…	…	…	…
Vibrio cholera	1 (1)	…	…	…	…	…	1 (6)
Aeromonas species	1 (1)	…	1 (3)	…	…	…	…
Gram-positive cocci							
Staphylococcus aureus	12 (9)	4 (16)	2 (6)	1 (7)	…	1 (7)	4 (23)
Enterococcus species	6 (4)	4 (16)	2 (6)	…	…	…	…
Streptococcus species	6 (4)	1 (4)	2 (6)	1 (7)	…	1 (7)	1 (6)
Aerococcus species	4 (3)	1 (4)	3 (9)	…	…	…	…
Rhodococcus equi	2 (1)	…	2 (3)	…	…	…	…
Streptococcus pneumoniae	1 (1)	…	…	1 (7)	…	…	…

Data are no. (%) of clinical cultures.

[a]Cerebrospinal fluid (CSF) specimens were obtained from 12 patients; cultures for 2 patients were mixed.

[b]Respiratory specimens were obtained from 13 patients; cultures from 2 patients were mixed.

MDR organisms (60 [91%]) were GNRs, representing 59% of all GNR isolates (see Supplementary Table 1 for complete source and resistance profiles). There were 43 Enterobacteriaceae isolates (75%) resistant to third-generation cephalosporins. Carbapenem resistance testing performed on 72 of 102 gram-negative isolates revealed that 27 (38%) were resistant to carbapenem. There were 4 gram-negative isolates resistant to all antibiotics tested other than colistin; 2 of 17 isolates (12%) were colistin resistant (Figure 2). Among 58 isolates from sources other than blood or CSF, 11 (16%) were not susceptible to any oral antibiotic. Of 12 *S. aureus* isolates, 6 (50%) were methicillin-resistant. None of the 6 enterococcus isolates were vancomycin resistant.

Three hundred and fifty-seven patients (23%) reported having received antibiotics ≤1 month prior to admission, and 324 (21%) reported having used them ≤1 week prior to admission.

Table 3. Species of Hospital-Onset Pathogenic Bacterial Isolates Recovered on Culture Among 105 Patients, by Clinical Specimen Cultured

Organism	Overall (n = 140)	Blood (n = 47)	CSF (n = 1)	Urine (n = 26)	Respiratory (n = 49)	Other (n = 17)
Gram-negative rods						
Escherichia coli	32 (23)	9 (19)	…	15 (58)	4 (8)	4 (23)
Acinetobacter species	26 (19)	14 (30)	1 (100)	…	10 (20)	1 (6)
Klebsiella species	20 (14)	3 (6)	…	1 (4)	15 (31)	1 (6)
Pseudomonas species	18 (13)	6 (13)	…	2 (8)	7 (14)	3 (18)
Citrobacter	13 (9)	3 (6)	…	7 (27)	3 (6)	…
Enterobacter	6 (4)	1 (2)	…	…	5 (10)	…
Unspecified	6 (4)	2 (4)	…	1 (4)	3 (6)	…
Gram-positive cocci						
Staphylococcus aureus	8 (6)	5 (11)	…	…	1 (2)	2 (12)
Enterococcus species	5 (4)	3 (6)	…	…	…	2 (12)
Streptococcus pneumoniae	1 (1)	1 (2)	…	…	…	…
Streptococcus species (other)	5 (4)	…	…	…	1 (2)	4 (23)

Data are no. (%) of clinical cultures.

Abbreviation: CSF, cerebrospinal fluid.

Table 4. Association of Clinical Factors With Multidrug Resistance Among 87 Patients With Community-Onset Gram-Negative Bacterial Infections

Risk Factor	Community-Onset Gram-Negative Bacterial Infections, No.	Multidrug Resistance, No. With Risk Factor (%)	Unadjusted OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*
Male sex	44	27 (61)	0.94 (.4–2.2)	1	0.85 (.33–2.16)	.73
Age						
<12 y	31	16 (52)	0.51 (.2–1.2)	.17	0.7 (.24–2.03)	.51
>50 y	22	16 (73)	1.89 (.7–5.5)	.31	1.29 (.38–4.63)	.69
HIV seropositive	12	6 (50)	0.37 (.1–1.4)	.17	…	
Diabetes mellitus	6	4 (67)	1.56 (.3–9.3)	1	…	
Severe malnutrition	4	2 (50)	1 (.1–8.3)	1	…	
Income <5000 rupees/mo[b]	56	38 (68)	1.98 (.8–4.9)	.17	…	
Vegetarian	17	11 (65)	1.15 (.4–3.5)	1	…	
Works with animals	20	16 (80)	3.05 (.9–10.1)	.07	3.14 (.96–12.39)	.07
Farmer	11	9 (82)	3.1 (.6–15.3)	.19	…	
Antibiotic use in past wk	16	13 (81)	3.17 (.8–12.1)	.09	…	
Antibiotic use in past mo	18	15 (83)	3.85 (1–14.5)	.05	4.17 (1.19–19.7)	.04
Prior visit to general practitioner	43	28 (65)	1.21 (.5–3.1)	.81	…	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for age, sex, and working with animals.

[b]For children, parental income is reported.

In a multivariable logistic regression model that adjusted for age, sex, and working with animals, antibiotic use ≤1 month prior to hospital admission was associated with increased odds of infection with a MDR clinical isolate (adjusted odds ratio [aOR], 4.17; 95% confidence interval [CI], 1.19–19.7; Table 4).

In-Hospital Outcomes

Patients with a culture-positive community-onset bacterial infection had a longer median hospital length of stay than culture-negative patients (5 vs 4 days; $P < .01$). A total of 119 of 1524 patients (8%) died during hospitalization. Of these 119 patients, 18 (15%) were found to have culture-positive community-onset infections, including 13 with bacteremia (2 also had positive results of a urine culture, and 1 had a positive result of a respiratory specimen culture), 1 had a positive respiratory specimen culture without bacteremia, and 1 each had positive results of CSF, pericardial, stool, and throat swab cultures. Among the 87 patients with a GNR isolate, 14 (16%)

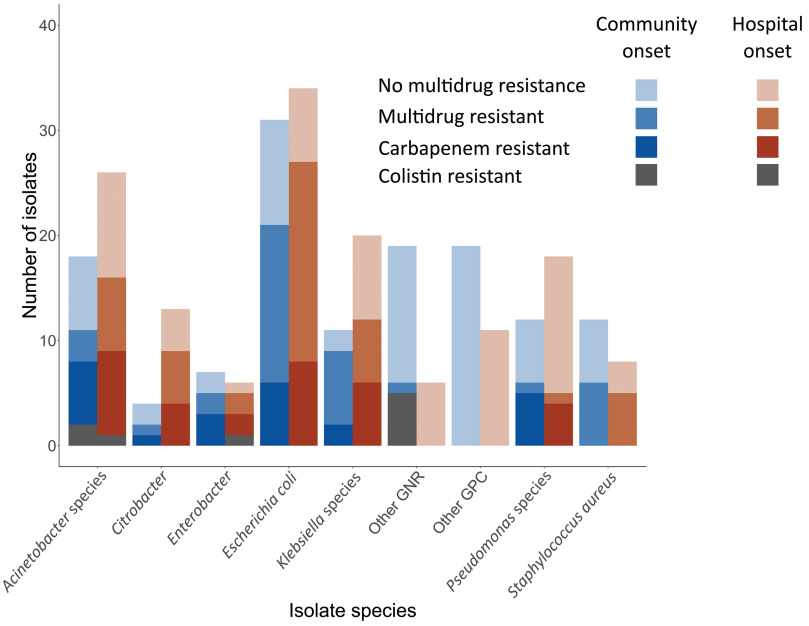

Figure 2. Total, multidrug-resistant, and carbapenem-resistant pathogenic bacterial isolates among adults and children with microbiologically infection by species and classification as community versus hospital onset. Blue bars represent community-onset bacterial infections, orange bars represent hospital-onset bacterial infections. Increasing shading intensity represents broader antimicrobial resistance. Abbreviations: GPC, gram-positive cocci; GNR, gram-negative rod.

died during hospitalization. In-hospital mortality was more common among patients with MDR GNR isolates (23%) than among those with drug-susceptible GNR isolates (6%; OR, 4.5; 95% CI, .9–12.6). In a multivariable logistic regression model that adjusted for age, sex, and diagnosis of pneumonia, bacteremia, meningitis, and urinary tract infection, isolation of a MDR GNR was independently associated with mortality (aOR, 6.1; 95% CI, 1.2–55.7).

DISCUSSION

The disease burden due to drug-resistant organisms is high among patients hospitalized for community-onset AFI in India [16]. Our study of 1524 adults and children hospitalized with AFI is among the largest prospective surveillance studies of community-onset antimicrobial resistance in India [17] and identifies a number of key findings. We report high overall antimicrobial resistance burden among microbiologically confirmed community-onset bacterial infections. Community-onset, carbapenem-resistant gram-negative bacterial infections were common, and isolates resistant to colistin were also detected [5]. We also observed a 5-fold increased risk of mortality associated with community-onset MDR GNR infections.

Only 4% of patients were found to have bacteremia, despite systematic and clinician-directed collection of blood specimens for culture. Although this is lower than the bacteremia rate in studies conducted in Africa, similar studies of patients with AFI in India and Southeast Asia have shown bacteremia in 0%–6% of patients [18–21]. Patients who received antibiotics prior to blood culture collection were less ill and more likely to be an adult but did not have any difference in frequencies of positive culture results as compared to patients who underwent collection of a blood specimen for culture prior to antibiotic administration. *E. coli* was only isolated in cultures of blood specimens that were collected after antibiotic administration, and all were unsurprisingly MDR. However, *Acinetobacter* was isolated in blood cultures performed before and after antibiotic administration in nearly equal proportions. Furthermore, administration of antibiotics prior to collection of blood specimens for culture was not significant when added to the model of clinical factors associated with community-onset, MDR gram-negative bacterial infection.

Consistent with other studies, *E. coli* was the most common causative gram-negative bacterium [2, 16, 22–24]. Notably, the second most common pathogen, *Acinetobacter baumannii,* is typically a hospital-acquired organism, yet it accounted for the majority of community-onset, MDR (particularly carbapenem-resistant) gram-negative bacterial infections. *Acinetobacter* appears to be a particularly prevalent infection in antimicrobial resistance studies in India. Furthermore, colistin-resistant gram-negative organisms and carbapenem-resistant organisms detected among community-onset bacterial infections indicate wide dissemination of MDR organisms in the environment in India [25]. Finally, as in other studies of *E. coli* and *Klebsiella pneumoniae* isolates from India [26–28], we found high rates of resistance to third-generation cephalosporins and fluoroquinolones. As third-generation cephalosporins are currently commonly used as empirical antibiotics for suspected serious bacterial infections, these findings have major implications for empirical antimicrobial choice in inpatient settings. Notably, we observed that a greater than expected proportion of carbapenem-resistant organisms were susceptible to fluoroquinolones, which is likely due to Indian prescribing practices that discourage routine fluoroquinolone use, to reserve these drugs for management of drug-resistant tuberculosis [29, 30].

In contrast to emerging data from India, however, we observed a relatively low rate of infection due to methicillin-resistant *S. aureus* [31, 32]. We also noted very low rates of invasive pneumococcal infections. Notably, nearly half of our study population received intravenous antibiotics before a blood culture was performed, and close to one third of patients received oral antibiotics prior to hospitalization, which may explain this finding.

As in prior studies, we also observed that antimicrobial exposure is a risk factor for subsequent infection due to MDR GNR [9, 33, 34] and that such infections lead to adverse outcomes, including increased length of hospitalization and mortality [35, 36]. In fact, we observed a 6-fold higher mortality among patients with MDR gram-negative bacterial infections. Increased in-hospital mortality has also been observed in another study in India focused on *Acinetobacter* bloodstream infections [37].

Our study highlights several unique population characteristics that may identify target populations with AFI with possible bacterial infections for whom empirical treatment regimens may differ. These include febrile patients who are older, patients with diabetes mellitus, and those with history of alcohol abuse and lower income. We also observed a high rate of HIV infection (13%) among adult febrile patients with bacterial infections as compared to the community HIV infection rate of 0.21%. This is in part because our site has a collocated HIV treatment center on its premises and caters to a predominantly poor, urban population. Although our study did not identify malnutrition as a risk factor for MDR bacterial infections in children, the fact that >58 000 neonatal deaths are estimated to be attributed to drug-resistant infections should inform that this vulnerable group be adequately managed with local formulary antimicrobials.

Taken together, our findings underscore the critical need to implement an evidence based antimicrobial stewardship program [38, 39]. Because mechanisms of antimicrobial resistance differ by organism, commonly implemented unilateral preventive approaches, such as isolation precautions, cohorting, and screening for asymptomatic carriage, targeting single organisms may be inadequate [40, 41]. Further, protecting existing

antimicrobials against increasing resistance becomes a priority with increasing global antimicrobial consumption [3], the availability in India of inexpensive antibiotics without prescription, and the slow pace of new antimicrobial discovery. In India, the Chennai Declaration is an important step in this direction to scale up awareness among health professionals, policy makers, and the general public.

Our study has some limitations. This study does not reflect the overall epidemiology of bacterial infections and antimicrobial resistance patterns in the community because we enrolled patients hospitalized for AFI and thus selected for more–severely ill patients. In addition, we may have underestimated the burden of pathogenic bacterial infections. Although blood cultures were systematically performed for all participants, cultures from other sources were only performed according to the treating clinician's discretion. Carbapenem resistance testing was not uniformly performed for clinician-directed cultures, involving primarily sources other than blood. Further, a sizeable proportion of participants received prior antibiotics. Despite these limitations, our study is one of few prospectively evaluating the epidemiology and drug resistance patterns of community-onset bacterial infections among adults and children.

In conclusion, our results indicate a high burden of bacterial infections and resistance to commonly used antimicrobials among patients hospitalized for AFI. Our findings support the urgent need to regulate antimicrobial use in the community, as well as in healthcare settings, so that existing antimicrobials may be preserved to combat serious bacterial infections. Furthermore, there is a staggering lack of data on adverse consequences of MDR bacterial infections in low-income and middle-income countries, where the problem is substantial [16, 42, 43]. Future studies should assess the burden of bacterial infections and drug resistance patterns in outpatient settings, to inform the choice of empirical antibiotics; the risk factors associated with acquisition or emergence of resistance; long-term morbidity and mortality; the impact of drug-susceptible and drug-resistant organisms on quality of life; and the risk factors for infection with these organisms.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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V. M., An. K., D. K., Aa. K., JZ, AG conceived the study. V. M., A. C., An. K, San. K., D. K., R. B., V. D., Aa. K., P. R., San. K., S. J., Sav. K., J. S., C. V., U. B., V. K., and I. M. conducted the study and collected data. V. M., M. R., and I. M. performed data analyses. V. M. drafted the initial manuscript, and all authors assisted in the manuscript preparation and approved the manuscript. A. G. obtained funding for the study.

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