Antibiotic susceptibility of intra-abdominal infection isolates from Indian hospitals during 2008

Stephen P. Hawser,¹ Robert E. Badal,² Samuel K. Bouchillon,²
Daryl J. Hoban² and the SMART India Working Group†

Correspondence

Stephen P. Hawser
shawser@ihmainc.com

¹IHMA Europe Sàrl, Epalinges, Switzerland

²International Health Management Associates Inc., Schaumburg, IL, USA

A total of 542 clinical isolates of aerobic Gram-negative bacilli from intra-abdominal infections were collected during 2008 from seven hospitals in India participating in the Study for Monitoring Antimicrobial Resistance Trends (SMART). Isolates were from various infection sources, the most common being gall bladder (30.1 %) and peritoneal fluid (31.5 %), and were mostly hospital-associated isolates (70.8 %) as compared to community-acquired (26.9 %). The most frequently isolated pathogens were *Escherichia coli* (62.7 %), *Klebsiella pneumoniae* (16.7 %) and *Pseudomonas aeruginosa* (5.3 %). Extended-spectrum β -lactamase (ESBL) rates in *E. coli* and *K. pneumoniae* were very high, at 67 % and 55 %, respectively. Most isolates exhibited resistance to one or more antibiotics. The most active drugs were generally ertapenem, imipenem and amikacin. However, hospital-acquired isolates in general, as well as ESBL-positive isolates, exhibited lower susceptibilities than community-acquired isolates. Further surveillance monitoring of intra-abdominal isolates from India is recommended.

Received 23 March 2010

Accepted 7 June 2010

INTRODUCTION

Nosocomial infections continue to be a significant cause of morbidity and mortality in hospitals. Furthermore, such infections often result in a lengthy hospital stay, increasing use of antibiotics and increasing healthcare costs. Intra-abdominal infections (IAIs) represent some of the most frequently encountered nosocomial infections in the healthcare setting (Kirkland *et al.*, 1999; Wong, 1999). A wide range of antimicrobial agents is available and recommended for use in the treatment of IAIs. Failure to diagnose early and the use of inadequate therapies for the treatment of IAIs are suggested to more likely result in increased therapy failure and mortality rates (Berne *et al.*, 1982; Yellin *et al.*, 1985; Solomkin *et al.*, 1990; Mosdell *et al.*, 1991; Falagas *et al.*, 1996). Several antimicrobial agents recommended by the Infectious Diseases Society of America include ampicillin–sulbactam, ertapenem, imipenem, meropenem, piperacillin–tazobactam, cephalosporins used in combination therapy, and quinolones, usually in combination with metronidazole (Solomkin *et al.*, 2010). However, unnecessary or needlessly broad antibiotic therapies may result in the acquisition of intrinsically

drug-resistant organisms and selection of resistance within the hospital unit (Wilton *et al.*, 2002; Shlaes *et al.*, 1997).

Surveillance of nosocomial infections has been a fundamental component of infection control in the United States for several decades (Pittet, 2005). Many other countries (Gastmeier *et al.*, 2003; Geubbels *et al.*, 2000; Cooke *et al.*, 2000; Mertens *et al.*, 1994; Jodra *et al.*, 2006) have implemented similar programmes based upon the National Nosocomial Infection Surveillance Program from the United States, though not all countries have resources to run surveillance programmes that allow for the rapid dissemination of such data to hospitals. One such country is India, which in terms of IAIs represents a vast population for which many clinical isolates have demonstrated resistance to one or multiple antibiotics (Hawser *et al.*, 2009).

The current study describes the demographics and antibiotic susceptibilities of clinical isolates from India collected during 2008. The study was part of the Study for Monitoring Antimicrobial Resistance Trends (SMART), which is a global programme that tracks the susceptibilities of IAI pathogens and disseminates such surveillance data on a worldwide, regional and local basis, including countries for which limited or no local surveillance data are available.

METHODS

Clinical isolates. All clinical isolates were derived from IAI. Only one isolate per patient was accepted into the study. Gram-negative

†Members of the SMART India Working Group are listed in Acknowledgements.

Abbreviations: ESBL, extended-spectrum β -lactamase; IAI, intra-abdominal infection; SMART, Study for Monitoring Antimicrobial Resistance Trends.

aerobic and facultative bacteria were cultured from specimens from intra-abdominal body sites, e.g. appendix, peritoneum, colon, bile, pelvis and pancreas. The majority of intra-abdominal specimens were obtained during surgery, though some paracentesis specimens were also accepted. Isolates from blood, urine and perirectal abscesses were excluded. Of isolates from organ sources, 163 (30.1 % of all isolates) were from gall bladder, while from fluid sources, 171 (31.5 % of all isolates) were from peritoneal fluid. The remaining 208 isolates (38.4 % of all isolates) were from various sources for which the frequency of each was <7.5 %. The most commonly isolated species was *Escherichia coli* ($n=340$; 62.7 % of all isolates), followed by *Klebsiella pneumoniae* ($n=90$; 16.7 %) and *Pseudomonas aeruginosa* ($n=29$; 5.3 %). Of the 340 *E. coli* isolates, 228 or 67 % were extended-spectrum β -lactamase (ESBL)-positive. ESBL-positive *K. pneumoniae* made up 55 % of all *K. pneumoniae* isolates, while 60 % of *Klebsiella oxytoca* isolates were ESBL-positive though the actual numbers of the latter species were small.

Isolates were considered to be community-associated if they were recovered from a specimen taken less than 48 h after the patient was admitted to the hospital, and hospital-associated if the specimen was taken 48 or more hours after hospital admission. Overall, 542 clinical isolates were collected from seven sites in India during 2008. These included hospitals in geographically distinct cities of Bangalore, Hyderabad, Indore, Kolkata, Lucknow, Mumbai and Vellore. Isolates were identified to the species level at each site utilizing local laboratory methods, and were sent to a central laboratory in the United States (Laboratories International for Microbiological Studies, a subsidiary of International Health Management Associates, Inc., in Schaumburg, Illinois, USA) for confirmation of identification and antimicrobial susceptibility testing. Development of a centralized database of study results was managed by International Health Management Associates, Inc.

Antimicrobial susceptibility testing. MICs and quality control were determined using MicroScan dehydrated broth microdilution panels manufactured by Siemens Medical Solutions Diagnostics, following Clinical and Laboratory Standards Institute guidelines (CLSI, 2007, 2009). All antimicrobial agents were supplied by the panel manufacturer. The following antimicrobial agents were included on the panels with their dilution ranges (expressed in μg

ml^{-1} throughout this report): ertapenem, 0.03–4; imipenem, 0.06–8; ceftazidime, 0.5–32; ceftazidime–clavulanic acid, 0.12–16; cefoxitin, 2–16; ciprofloxacin, 0.25–2; amikacin, 4–32; levofloxacin, 0.5–4; cefotaxime, 0.5–128; cefotaxime–clavulanic acid, 0.12–16; piperacillin–tazobactam, 2/4–64/4; ampicillin–sulbactam, 2/2–16/2; and ceftriaxone, 1–32. *E. coli*, *K. pneumoniae* and *K. oxytoca* strains were classified as ESBL-positive if there was at least an eightfold reduction (i.e. three doubling dilutions) of MIC for ceftazidime or cefotaxime tested in combination with clavulanic acid versus their MICs when tested alone (CLSI, 2007).

RESULTS

During 2008, seven hospitals participated in the study. From these seven hospitals, 542 clinical isolates that met the inclusion criteria were collected, characterized and tested for susceptibility to the antibiotics listed above. All isolates were from IAI and originated from general surgery wards ($n=232$; 42.8 % of all isolates), general medical wards ($n=118$, 21.8 %) and surgical intensive care units ($n=55$; 10.1 %). The remaining 137 isolates (25.3 %) originated from eight other locations. Totals of 384 (70.8 %) and 146 (26.9 %) were hospital-associated or community-associated isolates, respectively. The hospital-versus community-associated status of the remaining 12 isolates (2.2 %) was unknown. The most commonly isolated species was *E. coli* ($n=340$; 62.7 % of all isolates), followed by *K. pneumoniae* ($n=90$; 16.6 %) and *P. aeruginosa* ($n=29$; 5.4 %) (Table 1). *Acinetobacter baumannii* (2.0 %), *Citrobacter freundii* (2.2 %), *Enterobacter cloacae* (1.8 %) and *K. oxytoca* (1.8 %) were less frequently isolated. The remaining 40 isolates (7.4 % of all isolates) comprised a total of 14 additional species.

Only ertapenem (95 %) and imipenem (97.1 %) exhibited a percentage susceptibility of >90 % against *E. coli* (Table 1). Susceptibility against ESBL-positive *E. coli* isolates was

Table 1. Percentages of intra-abdominal isolates susceptible to the antimicrobial agents used in this study

Species with fewer than 10 isolated strains are not reported. AK, Amikacin; A/S, ampicillin–sulbactam; CPE, ceftazidime; CTX, cefotaxime; FOX, cefoxitin; CAZ, ceftazidime; CAX, ceftriaxone; CP, ciprofloxacin; ETP, ertapenem; IMP, imipenem; LVX, levofloxacin; P/T, piperacillin–tazobactam; NB, no clinical breakpoint available.

Organism	No.	AK	A/S	CPE	CTX	FOX	CAZ	CAX	CP	ETP	IMP	LVX	P/T
<i>Escherichia coli</i>	340	84.4	18.2	34.4	31.8	69.4	33.5	31.8	16.5	95.0	97.1	16.2	70.6
<i>E. coli</i> , ESBL	228	77.6	2.6	2.2	0.9	59.2	3.5	0.9	7.0	92.5	95.6	6.6	59.7
<i>E. coli</i> , non-ESBL	112	98.2	50.0	100.0	94.6	90.2	94.6	94.6	35.7	100.0	100.0	35.7	92.9
<i>Klebsiella pneumoniae</i>	90	82.2	38.9	48.9	46.7	56.7	47.8	46.7	45.6	85.6	93.3	56.7	68.9
<i>K. pneumoniae</i> , ESBL	49	67.4	2.0	6.1	2.0	46.9	6.1	2.0	8.2	73.5	87.8	24.5	42.9
<i>K. pneumoniae</i> , non-ESBL	41	100.0	82.9	100.0	100.0	68.3	97.6	100.0	90.2	100.0	100.0	95.1	100.0
<i>Pseudomonas aeruginosa</i>	29	62.1	NB	58.6	NB	NB	75.9	NB	41.4	NB	82.8	41.4	82.8
<i>Citrobacter freundii</i>	12	91.7	33.3	75.0	50.0	8.3	50.0	50.0	66.7	100.0	100.0	75.0	83.3
<i>Acinetobacter baumannii</i>	11	9.1	18.2	9.1	9.1	NB	9.1	9.1	9.1	NB	18.2	18.2	9.1
<i>Enterobacter cloacae</i>	10	80.0	10.0	90.0	70.0	NB	70.0	70.0	70.0	90.0	100.0	70.0	70.0
<i>Klebsiella oxytoca</i>	10	70.0	40.0	50.0	40.0	50.0	40.0	40.0	40.0	80.0	90.0	50.0	70.0
<i>K. oxytoca</i> , ESBL	6	50.0	16.7	16.7	0.0	33.3	0.0	0.0	16.7	66.7	83.3	33.3	50.0
<i>K. oxytoca</i> , non-ESBL	4	100.0	75.0	100.0	100.0	75.0	100.0	100.0	75.0	100.0	100.0	75.0	100.0

reduced for all agents as compared to susceptibilities against all *E. coli* isolates, with only imipenem (95.6 %) and ertapenem (92.5 %) exceeding 90 % against all *K. pneumoniae* isolates. The highest susceptibilities were observed with imipenem (93.3 %), ertapenem (85.6 %) and amikacin (82.2 %). The same three agents were also the most active against ESBL-positive isolates, though their susceptibilities were reduced by 5–15 % as compared to all *K. pneumoniae* isolates. Isolates of *A. baumannii* were essentially pan-resistant (susceptibility range 9.1–18.2 %). *C. freundii* and *E. cloacae* exhibited susceptibilities of ≥ 90 % to only three of the 12 antibiotics, with the most active agents being imipenem, ertapenem and amikacin. While 60 % of *K. oxytoca* isolates were ESBL-positive, there were only six ESBL-positive isolates and a meaningful susceptibility analysis could not be done.

Hospital-associated *E. coli* isolates were generally less susceptible than community-associated isolates to antibiotics (Table 2). The most active agents were imipenem and ertapenem, which exhibited susceptibilities of 96.2 % and 93.6 % against hospital-associated isolates and 98 % and 99 % against community-associated isolates. The next most active agent was amikacin, which exhibited susceptibilities of 81.6 % (hospital-associated) and 91.8 % (community-associated). The three most active agents against ESBL-positive *E. coli* isolates were imipenem, ertapenem and amikacin, having percentage susceptibilities against hospital-associated isolates of 94.6, 91 and 74.1, respectively, compared to 98.3, 96.5 and 89.5 for community-associated isolates, respectively. By contrast, the majority of non-ESBL isolates from both hospital- and community-associated infections exhibited susceptibilities of >90 % for nine of the 12 antibiotics. Similar susceptibility patterns concerning hospital- and community-associated isolates were also observed for *K. pneumoniae* (Table 2). The most active agents were consistently imipenem, ertapenem and amikacin, which exhibited percentage susceptibilities of

92.2, 85.9 and 81.3 and 95.8, 83.3 and 83.3 against hospital-associated and community-associated isolates, respectively. This pattern was also maintained against most ESBL-positive isolates. Although ertapenem was less active against ESBL-positive isolates from community sources, the difference was not statistically significant ($P>0.05$). ESBL-negative isolates were generally susceptible to most antibiotics, with isolates from hospital-associated and community-associated infections exhibiting susceptibilities of ≥ 90 % to nine and ten antibiotics, respectively.

DISCUSSION

IAI pathogens from India were from 21 different species and mostly consisted of *E. coli*, *K. pneumoniae* and *P. aeruginosa*. The majority of isolates originated from several infection sources including gall bladder and peritoneal fluid, though other sources were also represented, albeit at a much lower frequency. Antibiotic susceptibility results showed that the majority of species demonstrated resistance to one or, in many cases, multiple antibiotics. Overall, the exceptions to this rule were the carbapenems ertapenem and imipenem, which were consistently the most active agents with susceptibilities for each close to or surpassing 90 % for most pathogens with clinical breakpoints.

A high proportion of *E. coli*, *K. pneumoniae* and *K. oxytoca* isolates were ESBL-positive, though the number of the latter was low ($n=10$). High ESBL rates from this SMART 2008 report further confirm observations from SMART 2007 (Hawser *et al.*, 2009). While SMART is a global surveillance programme, several local reports also describe ESBL rates in India. For example, Agrawal *et al.* (2008) reported ESBL rates of 22 % during 2006 among *E. coli* and *K. pneumoniae* isolates from a tertiary care hospital in Pune. Sinha *et al.* (2008) showed ESBL rates of 64.8 % in clinical isolates that were collected from infections from another tertiary care hospital in Jaipur. High ESBL rates

Table 2. Percentages of hospital (HA) and community-associated (CA) intra-abdominal susceptible isolates examined in this study

AK, Amikacin; A/S, ampicillin–sulbactam; CPE, cefepime; CTX, cefotaxime; FOX, cefoxitin; CAZ, ceftazidime; CAX, ceftriaxone; CP, ciprofloxacin; ETP, ertapenem; IMP, imipenem; LVX, levofloxacin; P/T, piperacillin–tazobactam.

HA/CA	Organism	No.	AK	A/S	CPE	CTX	FOX	CAZ	CAX	CP	ETP	IMP	LVX	P/T
HA	<i>E. coli</i>	234	81.6	16.7	30.3	29.1	65.4	29.5	29.1	15.8	93.6	96.2	16.2	66.7
CA	<i>E. coli</i>	98	91.8	23.5	43.9	39.8	78.6	44.9	39.8	18.4	98.0	99.0	16.3	79.6
HA	<i>E. coli</i> , ESBL	166	74.1	3.0	1.8	1.2	54.8	1.8	1.2	6.6	91.0	94.6	6.6	56.0
CA	<i>E. coli</i> , ESBL	57	89.5	1.8	3.5	0.0	68.4	8.8	0.0	8.8	96.5	98.3	7.0	68.4
HA	<i>E. coli</i> , non-ESBL	68	100.0	50.0	100.0	97.1	91.2	97.1	97.1	38.2	100.0	100.0	39.7	92.7
CA	<i>E. coli</i> , non-ESBL	41	95.1	53.7	100.0	95.1	92.7	95.1	95.1	31.7	100.0	100.0	29.3	95.1
HA	<i>K. pneumoniae</i>	64	81.3	34.4	42.2	42.2	57.8	42.2	42.2	39.1	85.9	92.2	51.6	64.1
CA	<i>K. pneumoniae</i>	24	83.3	50.0	66.7	58.3	50.0	62.5	58.3	62.5	83.3	95.8	70.8	79.2
HA	<i>K. pneumoniae</i> , ESBL	38	68.4	0.0	2.6	2.6	44.7	5.3	2.6	5.3	76.3	86.8	23.7	39.5
CA	<i>K. pneumoniae</i> , ESBL	10	60.0	10.0	20.0	0.0	50.0	10.0	0.0	20.0	80.0	90.0	30.0	50.0
HA	<i>K. pneumoniae</i> , non-ESBL	26	100.0	84.6	100.0	100.0	76.9	96.2	100.0	88.5	100.0	100.0	92.3	100.0
CA	<i>K. pneumoniae</i> , non-ESBL	14	100.0	78.6	100.0	100.0	50.0	100.0	100.0	92.9	100.0	100.0	100.0	100.0

such as those documented (Hawser *et al.*, 2009; Agrawal *et al.*, 2008; Sinha *et al.*, 2008) have emphasized the need for national and regional guidelines, and therapeutic policies in India in order to overcome antibiotic resistance (Lakshmi, 2008). Such national/regional cooperation and collaboration among clinicians and microbiologists would significantly benefit the development of guidelines for the implementation of appropriate and targeted antimicrobial therapy.

Hospital-associated isolates were generally more resistant than community-associated isolates to the antibiotics tested. Furthermore, such reduced susceptibility of hospital-associated isolates may be due to the higher percentages of ESBL-positive *E. coli* and *K. pneumoniae* isolates in the hospital-associated group compared to the community-associated group. ESBL-positive isolates are known to exhibit reduced susceptibility to many antibiotics (Solomkin *et al.*, 2010). Although some minor numerical differences were observed, ESBL-negative community- and hospital-associated isolates exhibited similar susceptibilities. It is important to note that there was no information available regarding previous exposure of the community-associated or hospital-associated isolates to antimicrobial agents. However, cycles of antibiotic treatment in the hospital setting, and eventual spread from patient to patient, may have resulted in higher resistance acquisition rates as compared to isolates originating from the community.

In conclusion, the data from the present study confirm the high ESBL rates among *E. coli*, *K. pneumoniae* and *K. oxytoca* IAI isolates and the associated resistance to multiple antibiotics, and highlight differences in susceptibility patterns between community-associated and hospital-associated isolates. Data from studies such as SMART could be useful in developing antimicrobial stewardship initiatives and prolonging the utility of available therapies.

ACKNOWLEDGEMENTS

The authors thank all of the investigators and centres involved in the study. Special thanks go to Dr Joseph Chow of Merck & Co. for his excellent scientific and editorial support. This study was funded by a grant from Merck Research Laboratories. International Health Management Associates Inc. (IHMA) is under contract with, and compensated by, Merck & Co. to manage the Study for Monitoring Antimicrobial Resistance Trends (SMART).

The members of the SMART India Working Group are: Bhaskar N. Chaudhuri, AMRI Hospitals, Kolkata, India; Camilla Rodrigues, P. D. Hinduja National Hospital and Medical Research, Mumbai, India; Ranganathan Iyer, Global Hospitals, Hyderabad, India; Sangeeta Joshi, Manipal Hospital, Bangalore, India; T. N. Dhole, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, India; Uma Sekar, Sri Ramachandra Medical College, Porur, India; V. Balaji, Christian Medical College, Vellore, India.

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