J Antimicrob Chemother 2017; **72**: 1364–1372
doi:10.1093/jac/dkw574 Advance Access publication 25 January 2017

Journal of Antimicrobial Chemotherapy

Epidemiology and susceptibility of pathogens from SMART 2011–12 Turkey: evaluation of hospital-acquired versus community-acquired urinary tract infections and ICU- versus non-ICU-associated intra-abdominal infections

Iftihar Koksal[1]*, Gurdal Yilmaz[1], Serhat Unal[2], Pinar Zarakolu[2], Volkan Korten[3], Lutfiye Mulazimoglu[3], Fehmi Tabak[4], Birgul Mete[4], Vildan Avkan Oguz[5], Zeynep Gulay[5], Emine Alp[6], Robert Badal[7] and Sibylle Lob[7]

[1]Karadeniz Technical University, Trabzon, Turkey; [2]Hacettepe University, Ankara, Turkey; [3]Marmara University, Istanbul, Turkey; [4]Istanbul University, Istanbul, Turkey; [5]Dokuz Eylul University, Izmir, Turkey; [6]Erciyes University, Kayseri, Turkey; [7]International Health Management Associates, Inc., Schaumburg, IL, USA

*Corresponding author. Department of Infectious Diseases, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey. Tel: +90 462 3775861; Fax: +90 462 3775344; E-mail: iftihar@yahoo.com

Received 22 May 2016; returned 17 September 2016; revised 24 October 2016; accepted 13 December 2016

Objectives: To describe the epidemiology and susceptibility of pathogens (including ESBL producers) from hospital-acquired (HA) versus community-acquired (CA) urinary tract infections (UTIs) and ICU- versus non-ICU-associated intra-abdominal infections (IAIs) in Turkey as a part of the SMART study.

Methods: For this report, Gram-negative pathogens (363 from UTIs and 458 from IAIs) were collected in 2011 and 2012 at six hospitals in Turkey. HA versus CA UTIs and ICU- versus non-ICU-associated IAIs were compared for the species isolated, percentage of ESBL-positive isolates by species and susceptibility for overall and individual Gram-negative species.

Results: *Escherichia coli* was the most common pathogen identified in HA (40.2%) and CA (73.9%) UTIs and ICU-associated (25.8%) and non-ICU-associated (43.3%) IAIs. The rate of ESBL-positive *E. coli* was significantly higher in HA than in CA UTIs (50.5% versus 38.2%, $P < 0.001$) and in non-ICU-associated than in ICU-associated IAIs (52.5% versus 29.2%, $P = 0.029$). Of the drugs studied, only amikacin was active against ≥90% of pathogens in UTIs, while ertapenem, imipenem and amikacin were active against ≥90% of *E. coli*; and imipenem, amikacin and cefoxitin were active against ≥90% of *Klebsiella pneumoniae* in IAIs.

Conclusions: Our findings demonstrated that *E. coli* continues to be the principal pathogen of UTIs and IAIs in Turkey. Along with a high rate of ESBL-positive isolates, high antimicrobial resistance among Gram-negative bacilli from either UTIs or IAIs was noted particularly in the case of HA UTIs and ICU-associated IAIs, with a higher likelihood of carbapenem- or amikacin-based therapy to provide the broadest activity against bacterial pathogens.

Introduction

The Enterobacteriaceae, including *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Citrobacter* spp. and *Enterobacter* spp., is the family most commonly implicated in the aetiology of both urinary tract infections (UTIs) and intra-abdominal infections (IAIs).[1–3] Over the last decade, a dramatic increase has occurred in the worldwide prevalence of ESBL-positive Enterobacteriaceae, which frequently show resistance to several antibiotic classes, including fluoroquinolones and aminoglycosides,[4–6] and thus represent a challenge for practitioners, further limiting antibiotic therapy choices and adversely impacting patient outcomes.[6–8]

The choice of empirical antimicrobial therapy is guided by knowledge of the bacterial spectrum and the extent of antimicrobial resistance.[9,10] Given the global increase in antimicrobial resistance, particularly for Gram-negative bacteria, the variability in antimicrobial resistance in different geographical regions and over time, and the paucity of novel antibiotics in development, continuous surveillance of the pathogen prevalence including the prevalence of ESBL producers, as well as of the emergence and trends of

antimicrobial resistance, has been considered essential for guiding effective empirical therapy.[3,7,11]

The Study for Monitoring Antimicrobial Resistance Trends (SMART) is an ongoing global surveillance programme that has monitored the susceptibilities of Gram-negative bacilli from IAIs since 2002 and the susceptibilities of Gram-negative bacilli from hospitalized patients with UTIs since late 2009.[3]

This report describes the epidemiology and susceptibility of pathogens (including ESBL producers) from hospital-acquired (HA) versus community-acquired (CA) UTIs and ICU- versus non-ICU-associated IAIs in Turkey in 2011–12 as a part of the SMART programme.

Materials and methods

For this report, 363 Gram-negative pathogens from HA and CA UTIs and 458 Gram-negative pathogens from patients with IAIs in the ICU and non-ICU wards were collected in 2011 and 2012 at six hospitals in Turkey. Participating sites each collected up to 50 consecutive, non-selected aerobic or facultative Gram-negative pathogens from UTIs and up to 100 aerobic and facultative Gram-negative pathogens from the IAIs. Only one isolate per species per patient was accepted into the study.

HA versus CA UTIs and ICU- versus non-ICU-associated IAIs were compared in terms of the distribution of species isolated, percentage of phenotypically ESBL-positive isolates by species and the susceptibility for Gram-negative isolates overall and individual species.

A UTI was defined as HA or CA if cultured ≥48 h or <48 h post-admission, respectively. Isolates were identified to the species level and sent to a central lab [International Health Management Associates (IHMA), Inc., Schaumburg, IL, USA] for susceptibility testing and confirmation of identification. Organism collection, transport, confirmation of organism identification, susceptibility testing and the development and management of a centralized database were co-ordinated by IHMA, Inc. MICs were determined by the CLSI-recommended broth microdilution testing method using custom MicroScan panels (Beckman Coulter Inc.).[12] MIC interpretive criteria followed published guidelines of the CLSI.[13]

E. coli, *K. pneumoniae*, *K. oxytoca* and *P. mirabilis* isolates were classified phenotypically as ESBL producers if there was at least an 8-fold reduction of MIC for ceftazidime or cefotaxime tested in combination with clavulanic acid versus their MICs when tested alone.[13]

Quality controls were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding quality control results were within the acceptable ranges.[13]

Molecular characterization

Per SMART protocol, all ertapenem-non-susceptible Enterobacteriaceae and a random selection of about half of phenotypically ESBL-positive *E. coli*, *K. pneumoniae*, *K. oxytoca* and *P. mirabilis* isolates were molecularly characterized for β-lactamase genes. Genes encoding ESBLs (TEM, SHV, CTX-M, VEB, PER, GES), carbapenemases (KPC, NDM, IMP, VIM, OXA-48-like) and AmpC β-lactamases (CMY, DHA, FOX, MOX, ACC, MIR, ACT) were detected using a combination of microarray (Check-MDR CT101; Check-Points B.V.) and multiplex PCR assays as described previously.[14,15] Detected genes were sequenced and compared with the content of public databases. Carbapenemases were only detected among the ertapenem-non-susceptible isolates.

Ethics

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Karadeniz Technical University Medical Faculty Ethics Committee (24237859-462; 15 July 2015).

Statistical analysis

Data are expressed as number (*n*) and percentage (%). χ^2 test was used for comparisons. $P < 0.05$ was considered as the level of statistical significance.

Results

Distribution of species isolated in UTIs and IAIs

HA UTIs were caused by 14 species (40.2% *E. coli*; 22.5% *K. pneumoniae*; 10.0% *Pseudomonas aeruginosa*), while 9 species were found in CA UTIs (73.9% *E coli*; 13.0% *K. pneumoniae*; 4.3% *K. oxytoca*). *E. coli* isolates were significantly more common in CA than HA UTIs (73.9% versus 40.2%, respectively; $P < 0.001$), whereas *P. aeruginosa* (10.0% versus 2.2%; $P = 0.017$), *Acinetobacter baumannii* (5.9% versus 0%; $P = 0.017$) and *Serratia marcescens* (5.2% versus 0%; $P = 0.026$) were more common in HA than CA UTIs (Table 1).

The three most common species for ICU-associated IAIs were *E. coli* (25.8%), *A. baumannii* (23.7%) and *K. pneumoniae* (14.0%), and for the non-ICU-associated IAIs were *E. coli* (43.3%), *P. aeruginosa* (14.0%) and *K. pneumoniae* (13.2%). *E. coli* was significantly more common in non-ICU-associated IAIs ($P = 0.003$), whereas *A. baumannii* was more common in ICU-associated IAIs ($P < 0.001$) (Table 1).

Phenotypic ESBL rates for Gram-negative isolates

The rates for ESBL-positive *E. coli* were higher in HA than CA UTIs (50.5% versus 38.2%; $P < 0.001$) as well as in non-ICU- than ICU-associated IAIs (52.5% versus 29.2%; $P = 0.029$), while the rates for ESBL-positive *K. pneumoniae* were similar between the two types of UTI (44.3% versus 41.7% in HA and CA UTIs, respectively) and IAI (53.8% versus 39.6% in ICU and non-ICU wards, respectively) (Tables 2 and 3).

Susceptibility for Gram-negative isolates

For UTIs, susceptibility was lower in HA than in CA for the majority of the drugs studied. Of the drugs studied, only amikacin was active against ≥90% of both HA and CA pathogens when all Gram-negative pathogens were combined, and ertapenem, imipenem and cefoxitin were active against ≥90% of CA pathogens (Table 2 and Figure 1).

For IAIs, the susceptibility of *E. coli* was generally lower in non-ICU wards, while the reverse was true for *K. pneumoniae*, *A. baumannii* and *P. aeruginosa* with a lower susceptibility to antibiotics generally in ICU wards. Susceptibility of *A. baumannii* to imipenem and amikacin was remarkably low in ICU wards (18.2% and 22.3%, respectively), while *P. aeruginosa* was associated with 20% lower imipenem and amikacin susceptibility and 40% lower ciprofloxacin and levofloxacin susceptibility in ICU than in non-ICU wards (Table 3 and Figure 2).

Carbapenemase content of Enterobacteriaceae

The prevalence of detected carbapenemases among all Enterobacteriaceae was significantly different ($P = 0.03$) between

Table 1. Distribution of species isolated from patients with UTIs and IAIs in Turkey 2011–12

	UTIs, *n* (%)		IAIs, *n* (%)	
	HA (*n* = 271)	CA (*n* = 92)	ICU associated (*n* = 93)	non-ICU associated (*n* = 365)
E. coli	109 (40.2)	68 (73.9)**	24 (25.8)	158 (43.3)†
K. pneumoniae	61 (22.5)	12 (13.0)	13 (14.0)	48 (13.2)
P. aeruginosa	27 (10.0)	2 (2.2)*	11 (11.8)	51 (14.0)
A. baumannii	16 (5.9)	0 (0)*	22 (23.7)	31 (8.5)††
S. marcescens	14 (5.2)	0 (0)*	8 (8.6)	13 (3.6)
E. cloacae	13 (4.8)	1 (1.1)	2 (2.2)	20 (5.5)
K. oxytoca	9 (3.3)	4 (4.3)	2 (2.2)	9 (2.5)
P. mirabilis	8 (3.0)	1 (1.1)	3 (3.2)	9 (2.5)
Enterobacter aerogenes	6 (2.2)	1 (1.1)	2 (2.2)	6 (1.6)
Proteus vulgaris	0 (0)	2 (2.2)	0 (0)	0 (0)
Morganella morganii	0 (0)	1 (1.1)	2 (2.2)	8 (2.2)
Other	8 (3.0)		4 (4.3)	12 (3.3)

P value interpretations are as follows:
**$P < 0.001$ and *$P < 0.05$, compared with HA UTI isolates;
††$P < 0.001$ and †$P < 0.01$, compared with ICU-associated IAI isolates.

Table 2. ESBL positivity and antibiotic susceptibility rates for *E. coli*, *K. pneumoniae* and all Gram-negative isolates combined in HA versus CA UTIs

	n	ESBL (%)	ETP	IPM	AMK	FEP	CTX	FOX	CAZ	CRO	CIP	LVX	SAM	TZP
E. coli														
HA	109	**50.5***	**97.3**	**100**	**96.3**	54.1	48.6	**96.3**	58.7	49.5	49.5	49.5	22.0	82.6
CA	68	**38.2**	**98.5**	**100**	**97.1**	60.3	58.8	**92.7**	67.7	58.8	61.8	61.8	32.4	77.9
K. pneumoniae														
HA	61	**44.3**	80.3	86.9	**95.1**	60.7	47.5	80.3	62.3	55.7	63.9	70.5	27.9	63.9
CA	12	**41.7**	**100**	**100**	83.3	66.7	58.3	**100**	58.3	58.3	58.3	66.7	41.7	75.0
All Gram-negative														
HA	271		76.4	80.8	**90.0**	60.5	44.6	64.2	62.7	46.1	60.5	63.5	19.9	69.4
CA	92		**96.7**	**96.7**	**95.7**	64.1	57.6	**90.2**	69.6	55.4	62.0	63.0	32.6	75.0

ETP, ertapenem; IPM, imipenem; AMK, amikacin; FEP, cefepime; CTX, cefotaxime; FOX, cefoxitin; CAZ, ceftazidime; CRO, ceftriaxone; CIP, ciprofloxacin; LVX, levofloxacin; SAM, ampicillin/sulbactam; TZP, piperacillin/tazobactam.
Susceptibility of all Gram-negative species combined is shown using breakpoints appropriate for each species (0% susceptible assumed for species with no breakpoints for any given drug). Susceptibility values ≥90% are shown in bold and differences ≥10% between HA and CA isolates are underlined.
*$P < 0.001$ compared with CA UTIs.

HA and CA UTIs, with 12 carbapenemase-positive isolates among the 226 HA UTI Enterobacteriaceae isolates (5.3%) versus 0 of 90 CA UTI isolates. The 12 carbapenemase-positive UTI isolates comprised 10 *K. pneumoniae* isolates, 1 *E. coli* isolate and 1 *Enterobacter cloacae* isolate. All 12 isolates carried an OXA-48-like carbapenemase, with 1 isolate co-carrying a VIM-31 gene and 3 isolates co-carrying ESBLs. Among Enterobacteriaceae isolates from the IAIs, there was no significant difference ($P = 0.92$) between the rate of carbapenemase-positive isolates from the ICU and non-ICU wards, with 3.4% (2 of 58 isolates) and 3.2% (9 of 282 isolates) carbapenemase-positive isolates, respectively. The 11 carbapenemase-positive IAI isolates comprised 7 *K. pneumoniae* and 4 *E. coli* isolates. All 11 isolates carried an OXA-48-like carbapenemase with 3 isolates co-carrying an ESBL.

Discussion

Our findings based on the evaluation of Gram-negative pathogens from UTIs and IAIs from six hospitals in Turkey in 2011–12 revealed *E. coli* as the most common pathogen, followed by *K. pneumoniae* in UTIs and non-ICU-associated IAIs, and *A. baumannii* in ICU-associated IAIs. HA UTIs were associated with a lower prevalence of *E. coli* and a higher prevalence of *P. aeruginosa* and ESBL-positive *E. coli*, along with a lower susceptibility to

Table 3. ESBL positivity and antibiotic susceptibility rates for Gram-negative isolates in ICU versus non-ICU IAIs

	n	ESBL (%)	ETP	IPM	AMK	FEP	CTX	FOX	CAZ	CRO	CIP	LVX	SAM	TZP
E. coli														
ICU	24	29.2*	**100**	**95.8**	**95.8**	75.0	70.8	**91.7**	79.2	70.8	62.5	62.5	20.8	75.0
non-ICU	158	52.5	**96.2**	**98.1**	**96.8**	57.0	45.6	88.0	63.3	45.6	52.5	53.2	16.5	72.8
K. pneumoniae														
ICU	13	53.8	84.6	84.6	**100**	53.9	46.2	**100**	69.2	53.9	76.9	76.9	23.1	69.2
non-ICU	48	39.6	89.6	**93.8**	**95.8**	64.6	58.3	**100**	64.6	58.3	77.1	81.3	39.6	70.8
P. aeruginosa														
ICU	11			36.4	72.7	54.6			63.6		54.6	54.6		54.6
non-ICU	51			54.9	**94.1**	78.4			80.4		**92.2**	**92.2**		76.5
A. baumannii														
ICU	22			18.2	22.3	4.6	0		18.2	4.6	4.6	18.2	4.6	4.6
non-ICU	31			41.9	58.1	9.7	3.2		9.7	9.7	12.9	25.8	12.9	9.7

ETP, ertapenem; IPM, imipenem; AMK, amikacin; FEP, cefepime; CTX, cefotaxime; FOX, cefoxitin; CAZ, ceftazidime; CRO, ceftriaxone; CIP, ciprofloxacin; LVX, levofloxacin; SAM, ampicillin/sulbactam; TZP, piperacillin/tazobactam.
Susceptibility values ≥90% are shown in bold and differences ≥10% between ICU and non-ICU isolates are underlined. A blank space indicates that there is no breakpoint.
*$P < 0.05$ compared with non-ICU-associated IAIs.

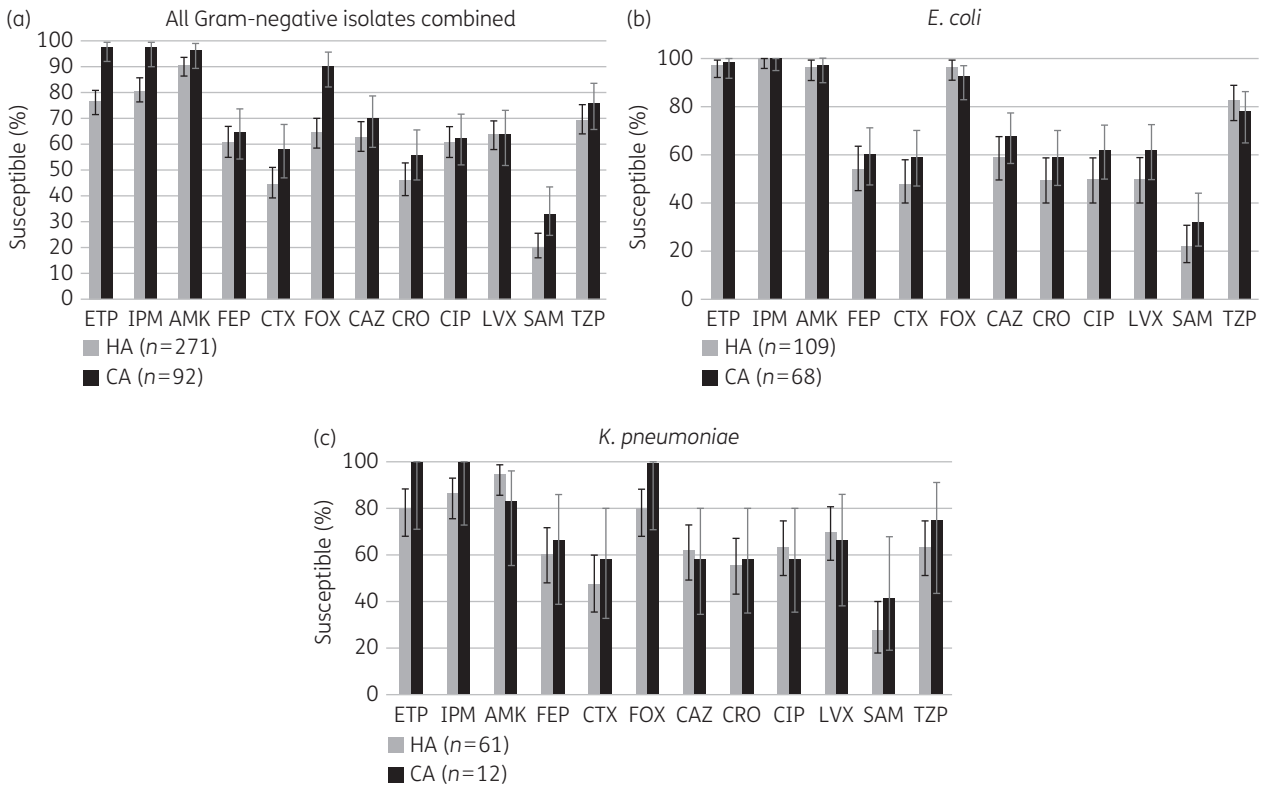

Figure 1. Susceptibility (with 95% CI) for (a) overall Gram-negative isolates and for (b) *E. coli* and (c) *K. pneumoniae* in HA versus CA UTIs in Turkey 2011–12. ETP, ertapenem; IPM, imipenem; AMK, amikacin; FEP, cefepime; CTX, cefotaxime; FOX, cefoxitin; CAZ, ceftazidime; CRO, ceftriaxone; CIP, ciprofloxacin; LVX, levofloxacin; SAM, ampicillin/sulbactam; TZP, piperacillin/tazobactam.

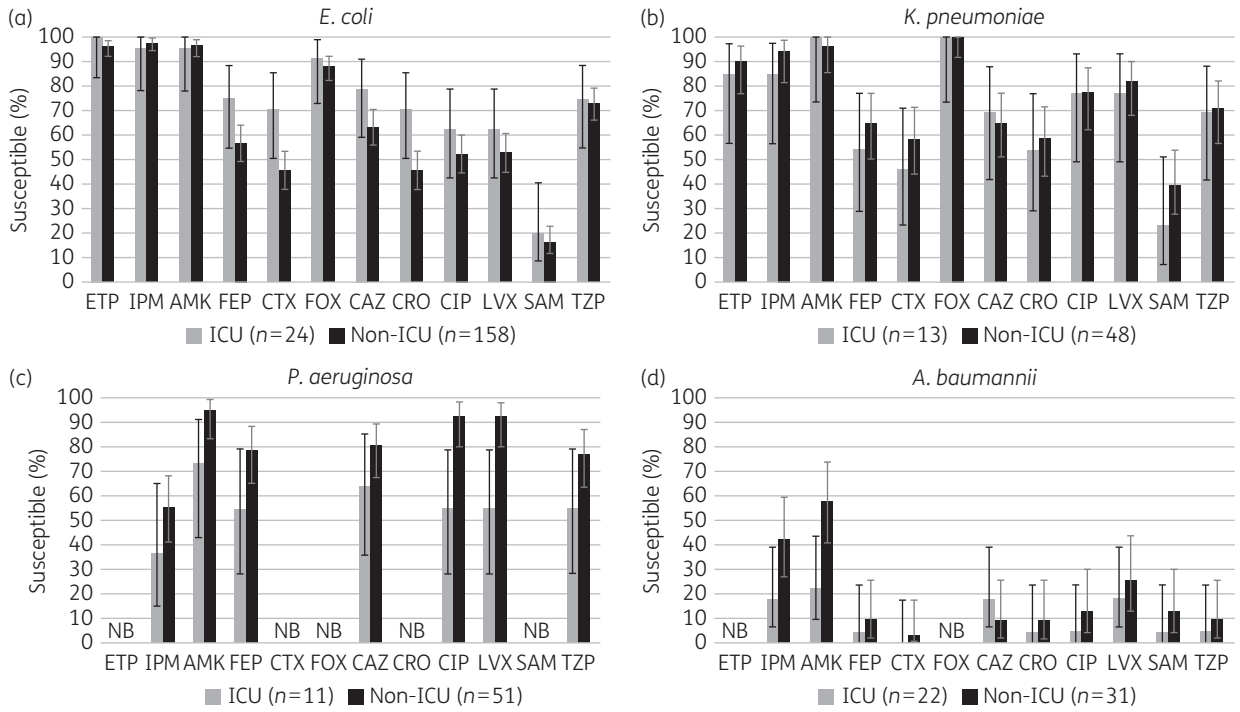

Figure 2. Susceptibility (with 95% CI) for (a) *E. coli*, (b) *K. pneumoniae*, (c) *P. aeruginosa* and (d) *A. baumannii* in ICU versus non-ICU IAIs in Turkey 2011–12. NB indicates that there is no breakpoint. ETP, ertapenem; IPM, imipenem; AMK, amikacin; FEP, cefepime; CTX, cefotaxime; FOX, cefoxitin; CAZ, ceftazidime; CRO, ceftriaxone; CIP, ciprofloxacin; LVX, levofloxacin; SAM, ampicillin/sulbactam; TZP, piperacillin/tazobactam.

the studied antibiotics. Considering IAIs, a higher prevalence of *E. coli* and higher rates of ESBL-positive *E. coli* along with the lower susceptibility of *E. coli* to the studied antibiotics were noted in non-ICU wards, whereas higher prevalence of *A. baumannii* and lower susceptibility of *K. pneumoniae* and *P. aeruginosa* were noted in the ICU wards. A very low susceptibility of *A. baumannii* was noted to all antibiotics in IAIs, and to imipenem and amikacin, in particular, in ICU wards. Overall, HA UTIs and ICU-associated IAIs were associated with a lower susceptibility to antibiotics. In general, amikacin, ertapenem, imipenem and cefoxitin were the most active agents in these settings.

Isolated species

UTIs

The analysis of global isolates from UTIs ($n = 24\,705$) from the 2009–11 SMART revealed *E. coli* (47.8%) to be the most frequently isolated species, followed by *K. pneumoniae* (14.5%) and *P. aeruginosa* (9.4%).[16] Likewise, in the current study the two most common species in both CA and HA UTIs were *E. coli* (40.2% and 73.9%, respectively) and *K. pneumoniae* (22.5% and 13.0%, respectively). Compared with CA UTIs, HA UTIs were caused by a greater variety of species, by a significantly smaller proportion of *E. coli* and a significantly larger proportion of *P. aeruginosa*, *A. baumannii* and *S. marcescens*.

IAIs

Data from the 2002–11 SMART studies conducted worldwide revealed that *E. coli* was the most common organism isolated from patients with IAIs, followed by *K. pneumoniae* and *P. aeruginosa*.[10,11,16–21] *E. coli*, *P. aeruginosa*, *K. pneumoniae* and *A. baumannii* were the four most common species isolated in IAIs in Turkey. The distribution of species differed between settings, with higher rates for *E. coli* in non-ICU wards and for *A. baumannii* in the ICUs. The prevalence of *A. baumannii* was also found to be high in the Middle East region compared with other regions in a recent SMART study, and a higher prevalence of *A. baumannii* was reported in the ICU than non-ICU wards in almost all studied geographical regions.[22]

Additionally, ICU stays have been reported to represent a risk factor for acquisition of *A. baumannii* infections.[23]

ESBL rates

UTIs

The increasing prevalence of ESBL-positive Enterobacteriaceae and the emergence of carbapenemase-producing isolates has been well-documented to be associated with increasing antimicrobial resistance in UTI pathogens from hospitalized patients.[24] The rate of ESBL-positive *E. coli* (50% versus 38%) was much higher in HA than CA UTIs in Turkey, while the rates for ESBL-positive *K. pneumoniae* (44% versus 42%) were similar regardless of the type of acquisition. These rates seem to be higher than those reported in previous SMART analyses in most global regions, ranging from 8.5% to 17.9% for *E. coli* and 8.8% to 38.9% for *K. pneumoniae*.[14,25]

Considering isolates from a variety of infection sources, high EBSL rates in Turkey were also reported in other studies, including the Tigecycline Evaluation and Surveillance Trial[26] on antimicrobial

susceptibility of Gram-negative and -positive bacteria collected across Eastern Europe between 2004 and 2010 (Turkey had the highest *E. coli* EBSL rate with 30.9%) and the Regional Resistance Surveillance study for 2011[27] on antimicrobial resistance patterns for selected European nations. (Turkey was among the European countries with the highest ESBL rates of >40.0%.)

IAIs

ESBL production has been increasingly recognized worldwide among Enterobacteriaceae strains.[11] Worldwide data from previous SMART analyses revealed regional differences in ESBL production rates for both *E. coli* (1.2%–64.9%) and *K. pneumoniae* (9.5%–46.8%), and a steady increase in ESBL production rates over time.[11,16,17,21,28–30] Rates for both ESBL-positive *E. coli* (52.5% in non-ICU, 29.2% in ICU) and *K. pneumoniae* (39.6% in non-ICU, 53.8% in ICU) strains were higher in Turkey compared with the 2005–07 global, 2009–10 global and 2002–11 European SMART rates described elsewhere,[17,28,29] and more consistent with regions with particularly high ESBL rates such as Asia, Latin America and the Middle East.[10,16,21,30]

Rates for ESBL-positive isolates also differed by setting in our study; similarly to other reports in the literature, ESBL-positive *K. pneumoniae* appeared more commonly in ICUs.[7] Accordingly, the susceptibility of *K. pneumoniae* was generally lower in ICU wards in the present study. On the other hand, ESBL-positive *E. coli* was less common in ICU wards in the current study, but the sample size was small.

Carbapenemase producers were detected among both UTI and IAI isolates, and all isolates carried OXA-48-like genes with one isolate co-carrying a VIM gene. This finding is consistent with reports describing a substantial increase in prevalence of OXA-48 producers in Turkey since the beginning of 2010s.[31] The geographical epicentre of Enterobacteriaceae carrying VIM enzymes is reported to be in nearby Greece.[31]

Susceptibility

UTIs

Susceptibility was almost always lower in HA UTIs than in CA UTIs in our study, even for *K. pneumoniae* for which the ESBL rates were similar in CA and HA infections. This was at least partly due to the carbapenemase-positive Enterobacteriaceae detected in isolates from HA UTIs, with almost all of them detected among *K. pneumoniae*.

Previous SMART studies revealed that ertapenem and imipenem were highly active against ESBL-producing strains of *E. coli*,[3,14,25] while these agents appeared less active against HA than CA isolates for ESBL-producing strains of *K. pneumoniae*.[3] Similarly, our findings revealed the high activity of ertapenem and imipenem against both *E. coli* and *K. pneumoniae* from CA UTIs, while slightly lower activity against *K. pneumoniae* was noted in the HA UTIs.

Hence, our findings support that *E. coli* and *K. pneumoniae* continue to be the principal pathogens of CA and HA UTIs and that the carbapenems and amikacin maintain a high level of activity against a wide range of Enterobacteriaceae with slightly higher resistance rates in HA UTIs caused by *K. pneumoniae*.[3,14]

Our findings are also consistent with data from the 2009–11 SMART programme in the USA[3] and the 2009–10 SMART programme in North America and Europe[14] in terms of resistance of Enterobacteriaceae to the fluoroquinolones ciprofloxacin and levofloxacin, as well as widespread resistance to ampicillin/sulbactam in UTIs. Low susceptibility to these agents and to cephalosporins, due in large part to high ESBL rates among *E. coli* and *K. pneumoniae*, have reduced therapeutic options for empirical UTI therapy to a limited list of drugs in Turkey, particularly in HA infections.

IAIs

Overall in Turkey, the susceptibility of the two most prevalent IAI pathogens (*E. coli* and *K. pneumoniae*) was low, with only ertapenem, imipenem and amikacin inhibiting ≥90% of *E. coli*, and imipenem, amikacin and cefoxitin inhibiting ≥90% of *K. pneumoniae* responsible for IAIs.

This seems consistent with data from previous SMART analyses that revealed continued efficacy of amikacin, ertapenem and imipenem against Gram-negative bacilli from patients with IAIs.[10,17,21,32]

Analysis of global trend data from 2002 to 2007 from the SMART study on IAIs revealed lower susceptibility of *E. coli* from HA than CA infections for all antimicrobial agents, apart from carbapenems.[33] Our findings related to lower susceptibility of *E. coli* in non-ICU than ICU wards should be interpreted with some caution because the sample size for ICU isolates was relatively small.

Our findings revealed very low susceptibility rates for imipenem against *A. baumannii* (18.2% in ICU wards, 41.9% in non-ICU wards) and *P. aeruginosa* (36.4% in ICU wards, 54.9% in non-ICU wards) from IAIs, particularly in ICU wards. A decline in susceptibility among *P. aeruginosa* and *Acinetobacter* spp. to imipenem was reported in the 2003–10 SMART programme on non-Enterobacteriaceae isolates from patients with IAIs in the Asia-Pacific region, particularly for HA pathogens.[34] In the 2010 data from the Comparative Activity of Carbapenem Testing (COMPACT) II study, 29.8% of *P. aeruginosa* and 73.0% of *A. baumannii* isolates were reported to be non-susceptible to at least one carbapenem.[35]

Notably, longitudinal data from the SENTRY Antimicrobial Surveillance Program revealed a significant increase in carbapenem-resistance rates among *A. baumannii* isolates collected in two Turkish medical centres during the 2000–06 period (20%–60%), largely driven by the dissemination of clones producing OXA-type carbapenemases.[36] In addition, Turkish data from the COMPACT study on the analysis of *in vitro* activities of carbapenems against clinical Gram-negative isolates obtained from ICU and non-ICU patients in 2008 revealed that, of 596 isolates, 188 (31.5%) were resistant to at least one of the carbapenems.[37]

Decreased activity of cephalosporins and quinolones with susceptibilities ranging from 50.0% to 88.5% against Gram-negative bacilli from patients with IAIs has been indicated to be an ever-increasing problem in previous SMART analyses, and is mirrored in the current study.[14,17,21,32,38] Data on levofloxacin and ciprofloxacin activity against *A. baumannii* (11.7% and 25.0% susceptible, respectively) in IAIs overall, and that of fluoroquinolones against *P. aeruginosa* (84.7% for both agents overall) particularly in non-ICU wards (92.2% for both agents) in our study are consistent with

a higher susceptibility to fluoroquinolones among *P. aeruginosa* (70%–80%)[4,34] than *Acinetobacter* spp. (<30%)[4] reported by previous US (2007–08)[4] and Asia-Pacific region (2003–10)[34] SMART analyses. When data from Turkey are compared with US (2007–08)[4] and Asia-Pacific region (2003–10)[34] SMART data, susceptibility of Gram-negative bacteria to fluoroquinolones in IAIs seems to be similar for *E. coli*, but slightly higher for *K. pneumoniae* and *P. aeruginosa*, particularly in non-ICU wards, and much lower for *A. baumannii* regardless of the ward type.

It should be noted that owing to the concerns of increasing resistance not only to fluoroquinolones but also to other antibiotics, fluoroquinolones have been recommended to be prescribed prudently and be restricted only to regions with ≥90% susceptibility rates.[11,39]

Based on our findings indicating high rates of resistance to cephalosporins, fluoroquinolones and β-lactam/β-lactam inhibitor combinations exhibited by the four studied IAI species, particularly by *A. baumannii* with very low susceptibility even to imipenem, therapeutic options for empirical treatment of IAIs are limited in Turkey. This is apparent particularly in ICUs where *A. baumannii* infections are more common and the susceptibility of *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* is generally lower than in non-ICU wards.

Turkey is currently the highest antibiotic consumer within the European region with 42.3 daily doses/1000 inhabitants per day (DID). Thus, the Turkish government has published a 'Rational Drug Use National Action Plan 2013–2017' with quantitative targets to reduce antibiotic use (by 2 DID annually between 2014 and 2017) and antimicrobial resistance.[40] In this regard, our findings provide baseline data on antibiotic resistance as well as guidance on rational drug use and antimicrobial stewardship programmes in Turkey. Surveillance studies such as SMART can and indeed have been used to inform guidelines for the treatment of infections, such as the SIS/IDSA guidelines for the diagnosis and management of complicated IAIs,[41,42] and continued surveillance in Turkey could be used to measure the impact of any interventions to reduce antibiotic use and antimicrobial resistance.

Certain limitations to this study should be considered. First, our sample sizes are small for some subsets of the data (resulting in large confidence intervals) and our findings lack documentation of trends of susceptibility patterns of Enterobacteriaceae, complete regional coverage and characterization of a full complement of antimicrobial agents. Second, lack of data on comparison of the activity of the different antimicrobials against ESBL-positive isolates seems to be another important limitation of the study. Nevertheless, our findings provide data on appropriateness of antimicrobial therapies to be confidently selected for evidence-based treatment of Gram-negative UTIs and IAIs in Turkish settings.

Conclusions

The present report on 2011–12 SMART data from Turkey demonstrates that *E. coli* continues to be the principal pathogen of UTIs and IAIs in Turkey and rates of ESBL-positive isolates and antimicrobial resistance among Gram-negative bacilli from both UTIs and IAIs are high, particularly for HA UTIs and ICU-associated IAIs. High ESBL rates among *E. coli* and *K. pneumoniae*, low susceptibility to fluoroquinolones and high rates of resistance exhibited by *A. baumannii* to most antimicrobial agents including imipenem in IAIs, mean that therapeutic options for empirical UTI and IAI therapy, particularly in HA UTIs and ICU-associated IAIs, are diminishing to a limited list of drugs in Turkey. Further monitoring of regional surveillance regarding the epidemiology and antimicrobial susceptibility profiles is needed to guide empirical antimicrobial therapy for UTIs and IAIs.

Acknowledgements

We thank all the participants in the SMART programme for their continuing contributions to its success.

Funding

Funding for the SMART programme was provided by Merck & Co., Inc. (Kenilworth, NJ, USA). International Health Management Associates (IHMA), Inc. manages the study on behalf of Merck & Co., Inc. The editorial support (see below) was funded by Merck Sharp & Dohme (MSD) Corp.

Transparency declarations

R. B. and S. L. work for IHMA, Inc., which receives funding from Merck & Co., Inc. to manage the SMART programme, including data analysis and publication. All other authors: none to declare.

Editorial support in the preparation of this manuscript was provided by Professor Sule Oktay, MD, PhD and Cagla Ayhan, MD from KAPPA Consultancy, Training and Research Ltd, Istanbul, Turkey.

References

1 Zhanel GG, DeCorby M, Adam H *et al*. Prevalence of antimicrobial-resistant pathogens in Canadian hospitals: results of the Canadian Ward Surveillance Study (CANWARD 2008). *Antimicrob Agents Chemother* 2010; **54**: 4684–93.

2 Nicoletti G, Nicolosi D, Rossolini GM *et al*. Intra-abdominal infections: etiology, epidemiology, microbiological diagnosis and antibiotic resistance. *J Chemother* 2009; **21** Suppl 1: 5–11.

3 Bouchillon SK, Badal RE, Hoban DJ *et al*. Antimicrobial susceptibility of inpatient urinary tract isolates of gram-negative bacilli in the United States: results from the study for monitoring antimicrobial resistance trends (SMART) program: 2009-2011. *Clin Ther* 2013; **35**: 872–7.

4 Hoban DJ, Bouchillon S, Hawser SP *et al*. Susceptibility of gram-negative pathogens isolated from complicated intra-abdominal infections in the United States 2007–2008: results of the SMART study. *Antimicrob Agents Chemother* 2010; **54**: 3031–4.

5 Hoban DJ, Bouchillon SK, Hawser SP *et al*. Trends in the frequency of multiple drug resistant Enterobacteriaceae and their susceptibility to ertapenem, imipenem, and other antimicrobial agents: data from the Study for Monitoring Antimicrobial Resistance Trends 2002 to 2007. *Diagn Microbiol Infect Dis* 2010; **66**: 78–86.

6 Osthoff M, McGuinness SL, Wagen AZ *et al*. Urinary tract infections due to extended-spectrum beta lactamase-producing gram-negative bacteria: identification of risk factors and outcome predictors in an Australian tertiary-referral hospital. *Int J Infect Dis* 2015; **34**: 79–83.

7 Dhillon R, Clark J. ESBLs: a clear and present danger? *Crit Care Res Pract* 2012; **2012**: 625170.

8 Falagas ME, Karageorgopoulos DE. Extended-spectrum β-lactamase-producing organisms. *J Hosp Infect* 2009; **73**: 345–54.

9 Bader MS, Hawboldt J, Brooks A. Management of complicated urinary tract infections in the era of antimicrobial resistance. *Postgrad Med* 2010; **122**: 7–15.

10 Yang Q, Wang H, Chen M *et al*. Surveillance of antimicrobial susceptibility of aerobic and facultative gram-negative bacilli isolated from patients with intra-abdominal infections in China: the 2002-2009 Study for Monitoring Antimicrobial Resistance Trends (SMART). *Int J Antimicrob Agents* 2010; **36**: 507–12.

11 Ko WC, Hsueh PR. Increasing extended-spectrum β-lactamase production and quinolone resistance among gram-negative bacilli causing intra-abdominal infections in the Asia/Pacific region: data from the Smart Study 2002-2006. *J Infect* 2009; **59**: 95–103.

12 Clinical Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Ninth Edition: Approved Standard M07-A9*. CLSI, Wayne, PA, USA, 2012.

13 Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-third Informational Supplement M100-S23*. CLSI, Wayne, PA, USA, 2013.

14 Hoban DJ, Lascols C, Nicolle LE *et al*. Antimicrobial susceptibility of Enterobacteriaceae, including molecular characterization of extended-spectrum β-lactamase-producing species, in urinary tract isolates from hospitalized patients in North America and Europe: results from the SMART study 2009-2010. *Diagn Microbiol Infect Dis* 2012; **74**: 62–7.

15 Kazmierczak KM, Lob SH, Hoban DJ *et al*. Characterization of extended-spectrum β-lactamases and antimicrobial resistance of *Klebsiella pneumoniae* in intra-abdominal infection isolates in Latin America, 2008-2012. Results of the Study for Monitoring Antimicrobial Resistance Trends. *Diagn Microbiol Infect Dis* 2015; **82**: 209–14.

16 Morrissey I, Hackel M, Badal R *et al*. A review of ten years of the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2002 to 2011. *Pharmaceuticals (Basel)* 2013; **6**: 1335–46.

17 Hawser SP, Bouchillon SK, Hoban DJ *et al*. In vitro susceptibilities of aerobic and facultative anaerobic gram-negative bacilli from patients with intra-abdominal infections worldwide from 2005-2007: results from the SMART study. *Int J Antimicrob Agents* 2009; **34**: 585–8.

18 Rossi F, Baquero F, Hsueh PR *et al*. In vitro susceptibilities of aerobic and facultative anaerobic gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). *J Antimicrob Chemother* 2006; **58**: 205–10.

19 Paterson DL, Rossi F, Baquero F *et al*. In vitro susceptibilities of aerobic and facultative gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends (SMART). *J Antimicrob Chemother* 2005; **55**: 965–73.

20 Baquero F, Hsueh PR, Paterson DL *et al*. In vitro susceptibilities of aerobic and facultatively anaerobic gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2005 results from Study for Monitoring Antimicrobial Resistance Trends (SMART). *Surg Infect (Larchmt)* 2009; **10**: 99–104.

21 Biedenbach DJ, Bouchillon SK, Hoban DJ *et al*. Antimicrobial susceptibility and extended-spectrum β-lactamase rates in aerobic gram-negative bacteria causing intra-abdominal infections in Vietnam: report from the Study for Monitoring Antimicrobial Resistance Trends (SMART 2009-2011). *Diagn Microbiol Infect Dis* 2014; **79**: 463–7.

22 Lob SH, Hoban DJ, Sahm DF *et al*. Regional differences and trends in antimicrobial susceptibility of *Acinetobacter baumannii*. *Int J Antimicrob Agents* 2016; **47**: 317–23.

23 Munoz-Price LS, Weinstein RA. Acinetobacter infection. *N Engl J Med* 2008; **358**: 1271–81.

24 Paterson DL. Resistance in gram-negative bacteria: Enterobacteriaceae. *Am J Med* 2006; **119**: 20–8.

25 Hoban DJ, Nicolle LE, Hawser S *et al*. Antimicrobial susceptibility of global inpatient urinary tract isolates of *Escherichia coli*: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program: 2009-2010. *Diagn Microbiol Infect Dis* 2011; **70**: 507–11.

26 Balode A, Punda-Polić V, Dowzicky MJ. Antimicrobial susceptibility of gram-negative and gram-positive bacteria collected from countries in Eastern Europe: results from the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) 2004-2010. *Int J Antimicrob Agents* 2013; **41**: 527–35.

27 Jones RN, Flonta M, Gurler N *et al*. Resistance surveillance program report for selected European nations (2011). *Diagn Microbiol Infect Dis* 2014; **78**: 429–36.

28 Badal R, Hawser S, Bouchillon S *et al*. Susceptibility and incidence of extended-spectrum β-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* in intra-abdominal infections globally: SMART 2009-2010. In: *Abstracts of the Twenty-first European Congress of Clinical Microbiology and Infectious Diseases, Milan, 2011*. Abstract P656. European Society of Clinical Microbiology and Infectious Diseases, Basel, Switzerland.

29 Lob S, Bouchillon S, Hackel M *et al*. Trends in susceptibility and ESBL production for *Escherichia coli* from intra-abdominal Infections: SMART 2002-2011. In: *Abstracts of the Fifty-second Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 2012*. Abstract C2-100. American Society for Microbiology, Washington, DC, USA.

30 Hsueh PR, Badal RE, Hawser SP *et al*. Asia–Pacific SMART Group. Epidemiology and antimicrobial susceptibility profiles of aerobic and facultative gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region: 2008 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). *Int J Antimicrob Agents* 2010; **36**: 408–14.

31 Tängdén T, Giske CG. Global dissemination of extensively drug-resistant carbapenemase-producing Enterobacteriaceae: clinical perspectives on detection, treatment and infection control. *J Intern Med* 2015; **277**: 501–12.

32 Hawser S, Hoban D, Bouchillon S *et al*. Antimicrobial susceptibility of intra-abdominal gram-negative bacilli from Europe: SMART Europe 2008. *Eur J Clin Microbiol Infect Dis* 2010; **30**: 173–9.

33 Hawser SP, Bouchillon SK, Hoban DJ *et al*. Epidemiologic trends, occurrence of extended-spectrum β-lactamase production, and performance of ertapenem and comparators in patients with intra-abdominal infections: analysis of global trend data from 2002-2007 from the SMART study. *Surg Infect (Larchmt)* 2010; **11**: 371–8.

34 Liu YM, Chen YS, Toh HS *et al*. In vitro susceptibilities of non-Enterobacteriaceae isolates from patients with intra-abdominal infections in the Asia-Pacific region from 2003 to 2010: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Int J Antimicrob Agents* 2012; **40** Suppl: S11–7.

35 Kiratisin P, Chongthaleong A, Tan TY *et al*. Comparative in vitro activity of carbapenems against major gram-negative pathogens: results of Asia-Pacific surveillance from the COMPACT II study. *Int J Antimicrob Agents* 2012; **39**: 311–6.

36 Gur D, Korten V, Unal S *et al*. Increasing carbapenem resistance due to the clonal dissemination of oxacillinase (OXA-23 and OXA-58)-producing *Acinetobacter baumannii*: report from the Turkish SENTRY Program sites. *J Med Microbiol* 2008; **57**: 1529–32.

37 Korten V, Söyletir G, Yalçın AN. [Comparative evaluation of in vitro activities of carbapenems against gram-negative pathogens: Turkish data of COMPACT study]. *Mikrobiyol Bul* 2011; **45**: 197–209. [Article in Turkish]

38 Chen WY, Jang TN, Huang CH *et al*. In vitro susceptibilities of aerobic and facultative anaerobic gram-negative bacilli isolated from patients with intra-abdominal infections at a medical center in Taiwan: results of the Study for

Monitoring Antimicrobial Resistance Trends (SMART) 2002–2006. *J Microbiol Immunol Infect* 2009; **42**: 317–23.

39 Solomkin JS, Mazuski JE, Bradley JS *et al*. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010; **50**: 133–64.

40 Versporten A, Bolokhovets G, Ghazaryan L *et al*. WHO/Europe-ESAC Project Group. Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. *Lancet Infect Dis* 2014; **14**: 381–7.

41 Hsueh PR, Hawkey PM. Consensus statement on antimicrobial therapy of intra-abdominal infections in Asia. *Int J Antimicrob Agents* 2007; **30**: 129–33.

42 Solomkin JS, Mazuski JE, Bradley JS *et al*. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010; **11**: 79–109.