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Managing adult patients with infectious diseases in emergency departments: international ID-IRI study

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Antimicrobial Original Research Paper

Managing adult patients with infectious diseases in emergency departments: international ID-IRI study

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We aimed to explore factors for optimizing antimicrobial treatment in emergency departments. A single-day point prevalence survey was conducted on January 18, 2020, in 53 referral/tertiary hospitals in 22 countries. 1957 (17%) of 11557 patients presenting to EDs had infections. The mean qSOFA score was 0.37 ± 0.74. Sepsis (qSOFA $\geq$ 2) was recorded in 218 (11.1%) patients. The mean qSOFA score was significantly higher in low-middle (1.48 ± 0.963) compared to upper-middle (0.17 ± 0.482) and high-income (0.36 ± 0.714) countries (**$P < 0.001$**). Eight (3.7%) patients with sepsis were treated as outpatients. The most common diagnoses were upper-respiratory ($n = 877$, 43.3%), lower-respiratory ($n = 316$, 16.1%), and lower-urinary ($n = 201$, 10.3%) infections. 1085 (55.4%) patients received antibiotics. The most-commonly used antibiotics were beta-lactam (BL) and BL inhibitors ($n = 307$, 15.7%), third-generation cephalosporins ($n = 251$, 12.8%), and quinolones ($n = 204$, 10.5%). Irrational antibiotic use and inappropriate hospitalization decisions seemed possible. Patients were more septic in countries with limited resources. Hence, a better organizational scheme is required.

Keywords: Emergency, infection, sepsis, treatment, antibiotic, elderly

Introduction

Infections make up a significant portion of patients presenting to emergency departments (ED), yet data on the impact of infectious diseases for the emergency clinicians are scarce. There are reports in the literature indicating that prevalence of infectious diseases in the EDs is on the rise, patients become more often septic, have more concomitant diseases and more risks for resistant infections.[1] There are rising concerns that individuals with

chronic infections like later stage HIV, tuberculosis, or hepatitis frequently apply to EDs since the primary care is weak[2] or migrants tend to use EDs as their primary source of care at the expense of primary care.[3] In principal, infectious diseases in EDs are commonly different from infections confronted inside the hospitals, predominantly from community-acquired origin. Culture and antimicrobial-susceptibility data are often not available during assessment, diagnoses are basically presumptive and treatments are mostly empirical.[4] Hence, there is a need to broaden our understanding of the impact of infectious diseases on the emergency department.

In this global international study, conducted on January 2020 well before the COVID-19 pandemic impacted ED epidemiological patterns worldwide, we aimed to explore a range of mechanisms to provide better harmonization of the clinical approaches including diagnostic and therapeutic perspectives in optimizing antimicrobial management. Hence, we evaluated infection types, their prevalences in the EDs, the severity of presenting patients, antibiotic use habits, and diagnostic challenges in a large geographical area.

Methods

This is an ID-IRI (Infectious Diseases International Research Initiative) point prevalence study, conducted on January 18, 2020. ID-IRI is an international platform, which serves as a network for clinical research on infectious diseases, and clinical microbiology (https://infectdisiri.com/). ID-IRI has more than 1000 members as clinical researchers worldwide and they voluntarily join the ID-IRI research projects. In this study, the referral/tertiary hospitals and the data of adult patients (≥18 years of age) were included solely.

Ethical issues

The ethical approval of the study was obtained from Medeniyet University, School of Medicine, Istanbul (2020/0113). The study was conducted according to the international guidelines of Strengthening the Reporting for Observational Studies in Epidemiology; STROBE.[5]

Participating medical centers

According to the income levels,[6] participating centers were categorized as lower-middle income (LMI) (Bangladesh, Egypt, India, Pakistan), upper-middle income (UMI) (Albania, Algeria, Bosnia and Herzegovina, Bulgaria, Iran, Kazakhstan, Lebanon, Romania, Turkey), and high income (HI) countries (Bahrain, Croatia, France, Israel, Italy, Poland, Saudi Arabia, Slovenia, Spain, United Arab Emirates). There seemed to be an algorithm in Spain and a guideline in Poland for antibiotic use in the EDs. For the rest of the countries national recommendations did not exist.

Data collection

The diagnosis of the patient was established by the attending doctor in the ED through a clinical evaluation and the laboratory analyses. The participant of the survey has assured the records to be complete and was in the ED in the study day checking the entire process. All centers were asked to provide qSOFA scores for all patients with infections applied to EDs and CURB-65 score for those with pneumonia. Patient databases and institutional data registries were reported through Google Drive. Two structured standardized questionnaires were used to collect data, one is for patients' and the other is for institutional data. No language barriers exist; no translation was requested. The data was collected and submitted by the participants, all were medical doctors, in the participating centers. They were asked to complete them at once, their responses were received, and merged as a single database, then analyzed. Prof. Hakan Erdem had access to responses/database through Google Drive solely to ensure data security. Repetitive emails were sent to participating centers to verify their responses and complete missing data if existed. Hakan Erdem will provide the database if the journal demands it.

Definitions

Elderly patients were defined as those over the age of 75 years.[7] **Anti-gram-positive agents** were defined as linezolid, daptomycin, tigecycline, vancomycin, and teicoplanin.[8] **Quinolones** were classified as old quinolones (ofloxacin, ciprofloxacin) and respiratory quinolones (levofloxacin, moxifloxacin, gemifloxacin) according to their spectrum of activity.[9] **Cephalosporins** were categorized in accordance with their traditional generations.[10] **Sepsis** was defined as a qSOFA score of ≥2,[11] **leukocytosis** as >11,000/mm^3, and **leucopenia** <4000/mm^3.[12] Febrile neutropenia was defined as a neutrophil count <500/ml in a febrile patient.[13] Pleuropulmonary and bronchial infections were categorized as **lower respiratory tract infections (RTI)** and **oropharyngeal and laryngeal infections** were recorded as upper respiratory infections. **Upper urinary tract** was defined as the pyelocaliceal system and the ureter while **lower urinary tract** included bladder, urinary sphincter, urethra, the prostate.

Statistical analysis

Descriptive values of numerical variables were computed as mean, standard deviation (SD),

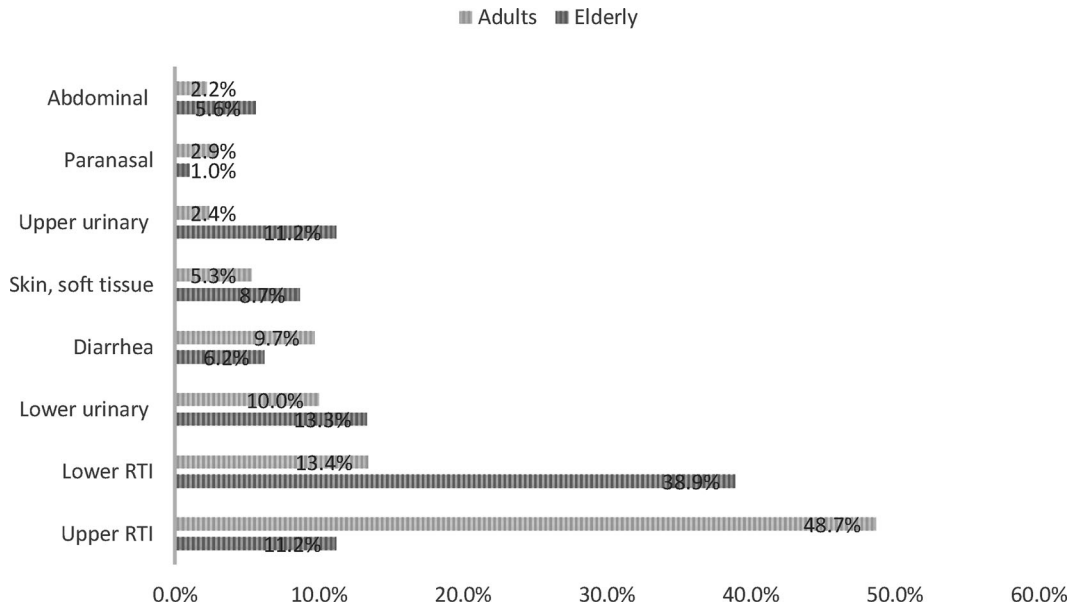

Figure 1. Distribution of common infections in the adults and the elderly. RTI: Respiratory tract infections.

median, 25th and 75th percentiles. Categorical variables were summarized as count and percent frequencies. The prevalence of infections in the EDs according to the countries was computed. For categorical variables, Fisher-Freeman-Halton exact test was used in the analysis of cross tables. When the significant relations are found between row and column variables, for each pair of columns, the column proportions were compared using a z test with Bonferroni adjustments. The effect of presence of comorbid conditions and ages of patients on qSOFA scores were evaluated by using Mann-Whitney U test. The differences among the income groups and among the infection types with regard to mean qSOFA score was evaluated by using Kruskal-Wallis test followed by Dunn test. The ED prevalence of infectious diseases patients among the countries were compared by using *t*-test for independent proportions. In all statistical analyses, SPSS (ver. 23) program was used and type-I error was accepted as 0.05.

Results

The study included 53 referral centers from 22 countries. The median number of overall patients applied to EDs in the participating hospitals was 117 (range 6–980). All participants submitted their data of patients with infections and the institutional data. Overall, 1957 (17%) out of 11557 total patients presenting to EDs had any type of infection. The mean age of the patients was 43.3 ± 20.4 and 989 (50.5%) were females. When the patients with infection were analyzed, 17 (0.9%) died, 101 (5.1%) taken to ICU, 418 (21.3%) hospitalized in the wards, 14 (0.7%) referred to another hospital, 3 (0.2%) refused hospitalization and 1406 (71.8%) were treated as outpatients ultimately.

Infectious syndromes

Upper RTIs were recorded in 877 (43.3%) patients [Pharyngitis ($n = 417$), tonsillitis ($n = 214$), common cold ($n = 130$), influenza like illness ($n = 115$), others ($n = 1$)]. Secondly, **Lower RTI** was observed in 316 (16.1%) patients [Pneumonia ($n = 218$), acute bronchitis ($n = 28$), chronic obstructive pulmonary disease (COPD) exacerbation ($n = 68$), others ($n = 2$)]. **Paranasal infections** ($n = 53$, 2.7%), **upper urinary infections** (pyelonephritis) ($n = 67$, 3.4%), **lower urinary tract infections** ($n = 201$, 10.3%), **diarrheal illnesses** ($n = 186$, 9.5%), **abdominal infections** ($n = 50$, 2.6%), **genital infections** ($n = 19$, 1%), **skin and soft tissue infections** ($n = 112$, 5.7%), **endovascular infections** ($n = 17$, 0.9%), **central nervous system (CNS) infections** ($n = 12$, 0.6%), **bone and joint infections** ($n = 12$, 0.6%), **abscess formation** (other than abdominal) ($n = 21$, 1.1%), **eye infections** ($n = 11$, 0.6%), **miscellaneous infectious diagnoses** ($n = 51$, 2.6%) cases were the other infections. Distribution of common infection diagnoses is presented in Figure 1.

Elderly group

There were 195 (10%) elders in this survey and there was a significant difference between age groups and the distribution of infections types (***P* < 0.001**). Lower RTI (39.0% vs. 13.4%), upper urinary infections (10.3% vs. 2.5%), intraabdominal infections (6.2% vs. 2.1%) were more common in the elders while upper RTI (10.8% vs. 47.8%) were more common in adults.

Antibiotic use patterns

1084 (9.4% of total ED applicants, 55.4% of those with infections) patients received 1115 antimicrobial drugs. Single antibiotic was given to 917 (46.8%) and combined antibiotics were prescribed to 167 (8.5%) patients. In 873 (44.6%) patients no antibiotic was recommended. Antibiotic groups used were beta lactam (BL) and BL inhibitors ($n = 307$, 15.7%; ampicillin-sulbactam, amoxicillin-clavulanic acid, piperacillin-tazobactam, cefuroxime axetil-clavulanic acid), third generation cephalosporins ($n = 251$, 12.8%; cefixime, cefdinir, cefpodoxime, ceftriaxone, cefotaxime, ceftibuten, cefditoren, ceftizoxime, ceftazidime, cefoperazone), old quinolones ($n = 114$, 5.8%; ofloxacin, ciprofloxacin), macrolides ($n = 101$, 5.2%; azithromycin, clarithromycin, spiramycin, dirithromycin), respiratory quinolones ($n = 91$, 4.6%; levofloxacin, moxifloxacin, gemifloxacin), second generation cephalosporins ($n = 63$, 3.2%; cefprozil, cefuroxime, cefaclor), carbapenems ($n = 58$, 3%; imipenem, meropenem, ertapenem), penicillins and penicillin derivatives ($n = 44$, 2.2%; penicillin G, penicillin V, flucloxacillin, cloxacillin, ampicillin, amoxicillin), metronidazole ($n = 43$, 2.2%), fosfomycin ($n = 41$, 2.1%), anti-Gram positive agents ($n = 37$, 1.9%; vancomycin, teicoplanin, linezolid, daptomycin, tigecycline), first generation cephalosporins ($n = 31$, 1.6%; cefazolin, cefadroxil, cefalexin), and aminoglycosides ($n = 19$, 1%; gentamicin, amikacin, tobramycin). Oseltamivir ($n = 11$), doxycycline ($n = 9$), fourth generation cephalosporins ($n = 9$, cefepime), clindamycin ($n = 9$), acyclovir ($n = 4$), rifampicin ($n = 4$), mupirocin ($n = 3$), furazolidone ($n = 3$), nitrofurantoin ($n = 3$), fifth generation cephalosporins [Cefradine ($n = 1$), ceftaroline ($n = 1$)], colistin ($n = 2$), ornidazole ($n = 2$), fluconazole ($n = 2$), voriconazole ($n = 2$), valacyclovir ($n = 1$), amphotericin-B ($n = 1$), anidulafungin ($n = 1$), terbinafine ($n = 1$) were used seldomly.

Antibiotic preferences in infection types

The use of common antibiotics in accordance with the infection types is presented in Table 1. The use of antibiotics has varied significantly according to infection types ($\boldsymbol{P = 0.0001}$). The most commonly used antibiotics in accordance with the diagnoses were: (i) **Upper RTI:** BL/BLI (47.8%), second-generation cephalosporins (11.2%), macrolides (13.2%). (ii) **Lower RTI:** Respiratory quinolones (20.2%), macrolides (14.5%). (iii) **Paranasal infections:** BL/BLI (70.3%). (iv) **Upper urinary infections:** Carbapenems (36.4%), old quinolones (21.2%), third-generation cephalosporins (18.2%). (v) **Lower urinary infections:** Old quinolones (45.7%). (vi) **Diarrhea:** Old quinolones (52.2%). (vii) **CNS infections:** Carbapenems (50%), penicillin derivatives (12.5%), macrolides (12.5%). (viii) **Intraabdominal infections:** Carbapenems (48.6%), third-generation cephalosporins (13.5%). (ix) **Endovascular infections:** Anti-Gram-positive agents (27.8%). (x) **Bone and joint infections:** First-generation cephalosporins (40%), second-generation cephalosporins (10%), penicillin derivatives (10%). (xi) **Skin and soft tissue infections:** BL/BLI (46.5%), First-generation cephalosporins (9.3%). (xii) **Genital infections:** Macrolides (13.3%), First-generation cephalosporins (6.7%). (xiii) **Abscesses:** BL/BLI (61.5%), First-generation cephalosporins (7.7%). (xiv) **Eye infections:** Aminoglycosides (90%). Fosfomycin was used in cystitis patients solely.

Antibiotic preferences in accordance with the economic status of the countries

The use of antibiotics in accordance with the economic status is presented in Table 2. There was a significant difference for antibiotic preferences in accordance with the economic status of the countries ($P < 0.001$). Third generation cephalosporins, carbapenems, and anti-Gram positive agents were used significantly more common in LMI countries while penicillin derivatives were consumed less commonly in these areas. Accordingly, first generation cephalosporins and old quinolones were used significantly more in UMI countries while BL/BLI were used more commonly in HI countries.

Antibiotics and outcomes

There were significant differences in using common antibiotics in accordance with the outcomes ($\boldsymbol{P < 0.01}$). (i) First and second-generation cephalosporins, BL/BLI, older quinolones, respiratory quinolones, macrolides were commonly used in outpatients. (ii) First-generation cephalosporins, respiratory quinolones, macrolides were used in those taken to the wards. (iii) Carbapenems, anti-Gram-positive agents, respiratory quinolones, and penicillin derivatives were used in patients taken to ICU. (iv) Third-generation cephalosporins were used in fatal cases. The infections and use of antibiotics in accordance with the outcomes are presented in Table 3.

Laboratory diagnosis

Microbiological diagnosis was applied in 178 (9.1%) patients. Urine ($n = 34$), blood ($n = 24$), sputum ($n = 22$), stool ($n = 6$), wound ($n = 11$), abscess ($n = 4$) cultures, and others ($n = 4$). Stool microscopy ($n = 20$), Gram stain ($n = 9$), CSF analysis ($n = 1$), influenza tests [$n = 11$; card test ($n = 7$),

Table 1. The distribution of common antibiotics used in accordance with the infection types

	1st Gen Cep		2nd Gen Cep		3rd Gen Cep		CARB		Pen Deriv.		BL/BLI		AGPA		Old Qn		Resp Qn		Macrolides		Aminoglc.		Total
Infections	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	**(*N*)**
Upper RTI	12	4.1	33	11.2	32	10.8	1	0.3	28	9.5	141	47.8	0	0.0	0	0.0	9	3.1	39	13.2	0	0.0	**295**
Lower RTI	1	0.3	10	3.0	99	29.9	23	6.9	4	1.2	57	17.2	14	4.2	6	1.8	67	20.2	48	14.5	2	0.6	**331**
Paranasal	0	0.0	1	2.7	5	13.5	2	5.4	0	0.0	26	70.3	1	2.7	1	2.7	1	2.7	0	0.0	0	0.0	**37**
Upper Urinary	1	1.5	3	4.5	24	36.4	12	18.2	1	1.5	3	4.5	1	1.5	14	21.2	5	7.6	1	1.5	1	1.5	**66**
Lower Urinary	1	0.9	7	6.0	32	27.6	5	4.3	2	1.7	7	6.0	1	0.9	53	45.7	4	3.4	3	2.6	1	0.9	**116**
Diarrheal illness	0	0.0	3	6.5	8	17.4	0	0.0	1	2.2	3	6.5	1	2.2	24	52.2	2	4.3	4	8.7	0	0.0	**46**
Intraabdominal	0	0.0	0	0.0	18	48.6	5	13.5	0	0.0	6	16.2	2	5.4	3	8.1	1	2.7	1	2.7	1	2.7	**37**
Genital infection	1	6.7	1	6.7	5	33.3	0	0.0	0	0.0	2	13.3	0	0.0	3	20.0	1	6.7	2	13.3	0	0.0	**15**
Skin, Soft tissue	8	9.3	3	3.5	12	14.0	5	5.8	4	4.7	40	46.5	8	9.3	4	4.7	0	0.0	1	1.2	1	1.2	**86**
Bone and Joint	4	40.0	1	10.0	0	0.0	0	0.0	1	10.0	2	20.0	0	0.0	2	20.0	0	0.0	0	0.0	0	0.0	**10**
Endovascular	0	0.0	0	0.0	4	22.2	1	5.6	1	5.6	5	27.8	5	27.8	0	0.0	0	0.0	0	0.0	2	11.1	**18**
CNS	0	0.0	0	0.0	4	50.0	0	0.0	1	12.5	0	0.0	1	12.5	0	0.0	0	0.0	1	12.5	1	12.5	**8**
Abscess formation	1	7.7	0	0.0	2	15.4	0	0.0	1	7.7	8	61.5	0	0.0	1	7.7	0	0.0	0	0.0	0	0.0	**13**
Eye	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	10.0	0	0.0	0	0.0	9	90.0	**10**
Miscellaneous	2	7.4	1	3.7	5	18.5	4	14.8	0	0.0	7	25.9	3	11.1	2	7.4	1	3.7	1	3.7	1	3.7	**27**
TOTAL	**31**		**63**		**250**		**58**		**44**		**307**		**37**		**114**		**91**		**101**		**19**		**1115**

RTI: Respiratory tract infection, CNS: Central nervous system, Gen Cep: Generation cephalosporins, CARB: Carbapenems, Pen Deriv.: Penicillins and derivatives, BL/BLI: Beta lactam and beta lactam inhibitors, AGPA: Anti-Gram positive agents, Qn: Quinolones, Resp: Respiratory, Aminoglc: Aminoglycosides.

Table 2. The use of antibiotics and outcomes in accordance with the economic status

	LMI Countries		UMI Countries		HI Countries		Total
Microbiological diagnosis	***n***	%	***n***	%	***n***	%	***n***
• Not done	201_a	81.7	1236_b	93.5	342_c	87.9	1779
• Applied	45_a	18.3	86_b	6.5	47_c	12.1	178
Total	**246**		**1322**		**389**		**1957**
***P* value**	**<0.001**						
Antibiotics subgroups used							
First Gen Cep	2_a	1.0	29_b	4.5	0_a	0.0	31
Second Gen Cep	8	3.9	37	5.7	18	6.7	63
Third Gen Cep	76_a	37.4	129_b	20.0	45_b	16.9	250
Carbapenems	34_a	16.7	15_b	2.3	9_b	3.4	58
Penicillin derivatives	3_a	1.5	31_b	4.8	10_b	3.7	44
BL/BLI	16_a	7.9	191_b	29.6	100_c	37.5	307
AGPA	20_a	9.9	8_b	1.2	9_c	3.4	37
Old Quinolones	13_a	6.4	82_b	12.7	19_a	7.1	114
Respiratory Quinolones	16	7.9	53	8.2	22	8.2	91
Macrolides	13	6.4	61	9.5	27	10.1	101
Aminoglycosides	2	1.0	9	1.4	8	3.0	19
Total	**203**		**645**		**267**		**1115**
***P* value**	**<0.001**						
Outcomes							
Died	11_a	4.5	1_c	0.1	5_b	1.3	17
Hospitalized in ICU	62_a	25.2	30_b	2.3	9_b	2.3	101
Hospitalized in the ward	133_a	54.1	142_b	10.7	141_c	36.2	416
Referred to another hospital	2	0.8	7	0.5	5	1.3	14
Refused hospitalization	0	0.0	1	0.1	2	0.5	3
Treated as outpatient	38_a	15.4	1141_b	86.3	227_c	58.4	1406
Total	**246**		**1322**		**389**		**1957**
***P* value**	**<0.001**						

LMI: Lower-middle income, UMI: Upper-middle-income, HI: High income, Gen Cep: Generation Cephalosporins, AGPA: Anti-Gram positive agents.

Each different subscript letter denotes a subset of income categories whose column proportions significantly differ significantly from each other at the .05 level.

GeneXpert ($n=4$)], PCR testing ($n=12$), Rose-Bengal test ($n=2$), immunochromatography for *Streptococcus pyogenes* ($n=6$), virus isolation ($n=2$), urine pneumococcal antigen test ($n=1$), MALDI-TOF Mass Spectrometry ($n=1$). In 448 (45.3%) out of 988 patients white blood cell count (WBC) was reported, there was leukocytosis and in 58 (5.9%) patients leucopenia was detected. The median of WBC was 10200 cells/ml (IQR, 7300-14000).

The microbiological diagnosis was applied more frequently in LMI countries (18.3%) than HI (12.1%), which is followed by UMI (6.5%) countries (**$P<0.001$**) (Table 2).

Severity status

The mean qSOFA score of the patients was 0.37 ± 0.74. The distribution of the scores was as follows: 0 ($n=1494$, 76.3%), 1 ($n=247$, 12.6%), 2 ($n=167$, 8.5%), 3 ($n=49$, 2.5%). The mean qSOFA score was significantly higher in LMI countries (1.48 ± 0.963) compared to UMI (0.17 ± 0.482) and HI (0.36 ± 0.714) countries (**$P<0.001$**). The outcomes in accordance with the economic status are presented in Table 2. Accordingly, mortality and hospitalizations in the ICUs were significantly higher in LMI countries (**$P<0.001$**) while patients treated as outpatients were significantly lower (**$P<0.001$**). The elders (0.98 ± 0.989) had higher qSOFA scores compared to the adults (0.30 ± 0.678) (**$P<0.001$**). There were significant differences in qSOFA scores for the infection types (**$P=0.0001$**). Upper urinary infections, lower RTI, endovascular infections, CNS infections > intraabdominal infections > bone and joint infections > skin and soft tissue infections > diarrhea > genital infections > lower urinary infections > abscesses > paranasal infections > upper RTI > eye infections. Accordingly, there were significant differences in qSOFA scores for ultimate outcomes in the EDs (**$P=0.0001$**). Fatal cases, hospitalized in the ICUs > refused hospitalization, referred to another hospital, hospitalized in the ward > treated as outpatients. When no antibiotic is prescribed qSOFA was significantly lowest, when single antibiotic was given it was moderate and when antibiotic combinations were preferred qSOFA was significantly higher (**$P=0.0001$**). When HIV infection ($n=2$) and asplenia/hyposplenism ($n=3$) were excluded due to small numbers, qSOFA was significantly higher in the presence of comorbidities (**$P=0.0001$ for all**). Distribution of qSOFA scores in accordance with the therapeutic approach, infection types, ultimate outcomes, comorbidities in the emergency departments are presented in Table 4.

Table 3. The infections and use of antibiotics in accordance with the outcomes

	Hospitalized												
	Died		ICU		Ward		Referred to other centers		Refused hospitalization		Outpatients		Total
Infections	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***N***
Upper RTI	–	–	5	4.1	48	11.5	3*	21.4	1	33.3	820	58.3	**877**
Lower RTI	7	41.2	61	60.4	140	33.6	5	35.7	1	33.3	102	7.3	**316**
Paranasal	–	–	1	0.8	2	0.50	1		–	–	49	3.5	**53**
Upper Urinary	–	–	10	9.9	36	8.6	–	–	–	–	19	1.4	**67**
Lower Urinary	2	11.8	7	6.9	27	6.5	–	–	–	–	167	11.9	**201**
Diarrheal illness	–	–	2	2	44	10.6	–	–	–	–	138	9.8	**184**
Intraabdominal	1	5.9	3	3	35	8.4	4	28.6	1	33.3	6	0.4	**50**
Genital infection	–	–	1	1	5	1.2		–	–	–	13	0.9	**19**
Skin Soft tissue	1	5.9	3	3	45	10.8	2	14.3	–	–	61	4.3	**112**
Bone and Joint	–	–	–	–	10	2.4	–	–	–	–	2	0.1	**12**
Endovascular	4	23.5	2	2	8	1.9	–	–	–	–	3	0.2	**17**
CNS	–	–	6	5.9	5	1.2	–	–	–	–	–	–	**11**
Abscess formation	–	–	–	–	7	1.7	–	–	–	–	14	1	**21**
Eye	–	–	–	–	–	–	–	–	–	–	11	0.8	**11**
Miscellaneous	–	–	6	5.9	26	6.3	–	–	–	–	18	1.3	**51**
Total (patients)	**17**		**101**		**416**		**14**		**3**		**1406**		**1957**
Use of common antibiotics and in accordance with the outcomes													
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***
1st Gen Cep	–	–	–	–	11_a	2.6	–	–	–	–	20_a	1.4	**31**
2nd Gen Cep	–	–	–	–	13	3.1	–	–	–	–	50_a	3.5	**63**
3rd Gen Cep	9_a	52.9	32	31.7	116	27.8	3	21.4	2	66.7	88	6.3	**250**
Carbapenems	3	17.6	32	31.7_a	23	5.5	–	–	–	–	–	–	**58**
Penicillin and derivatives	–	–	2	2	6	1.4	–	–	–	–	36_a	2.6	**44**
BL/BLI	1	5.9	12	11.9	65	15.6	2	14.2	–	–	227_a	16.1	**307**
AGA	1	5.9	19_a	18.8	17	4	–	–	–	–	–	–	**37**
Old Quinolones	–	–	5	5	18	4.3	1	7.1	–	–	90_a	6.4	**114**
Respiratory Quinolones	1	5.9	11_a	10.9	27_a	6.5	–	–	–	–	52_a	3.7	**91**
Macrolides	–	–	5	5	26_a	6.2	2_a	14.2	–	–	68_a	4.8	**101**
Aminoglycosides	–	–	3	3	7	1.7	–	–	–	–	9	0.6	**19**
Total (patients)	**17**		**101**		**416**		**14**		**3**		**1406**		**1957**

ICU: Intensive care unit, RTI: Respiratory tract infections, CNS: Central nervous system infections, Gen Cep: Generation cephalosporins, BL/BLI: Beta lactam and beta lactam inhibitors, AGA: Anti-Gram positive agents.
*There are coexistent diagnoses and combined antibiotic uses which both may be different from the number of patients.

Sepsis patients

Sepsis (qSOFA $\geq$2) was recorded in 218 (11.1%) patients. Among them 14 (6.4%) died, 74 (33.9%) taken to ICU, 121 (55.5%) hospitalized in the wards, 1 (0.5%) referred to another hospital, and 8 (3.7%) were treated as outpatients. Blood cultures were obtained in the EDs in 22 (10.1%) of sepsis patients. The diagnoses of patients with sepsis are presented in Figure 2.

Prevalence of infectious disease

The overall prevalence of infectious diseases patients applied to EDs in the study was 17%. The ED prevalences of infections across the countries are presented in Table 5. There were significant differences in prevalences between the country groups (***P*<0.001**). Upper RTI [UMI (55.1%) >HI (30.8%) >LMI (4.5%)], lower RTI [LMI (41.1%) >HI (23.4%) >UMC (9.4%)], upper urinary infections [LMI (5.7%) >UMI (2.8%)], and diarrheal illnesses [LMI (11.8%), UMI (9.6%) >HI (5.7%)] had significant differences for the prevalences. But there was not any difference for lower urinary infections [LMI (6.9%), UMC (10.6%), HI (9.8%)].

Discussion

In this international study the prevalence of patients with infections applied to EDs was found to be 17% [mean age 40; 50% female]. We have shown that most common infections observed in EDs were RTIs extending from upper (43.3%) to lower respiratory (16.1%) tracts. Urinary tract infections (13.7%) in which one fourth presented as pyelonephritis, and diarrheal illnesses (9.5%) followed RTIs. Although the mean qSOFA score (0.37 ± 0.74) was low, the patients with pneumonia, pyelonephritis, endovascular and CNS infections were the most critical cases. In LMI countries infections in the ED was significantly more severe, led to death and ICU admittance more frequently compared to richer countries. Basically, LMI countries experienced more problematic lower RTIs, pyelonephritis, and diarrheal illnesses, and although insufficient in the entire participating countries, microbiological tests were applied

Table 4. Distribution of qSOFA scores in accordance with the therapeutic approach, infection types, ultimate outcomes, comorbidities in the emergency departments

	N	Mean	Std. Deviation	Minimum	Maximum	25th	Median	75th
Antibiotic use								
None	873	.20	.571	0	3	.00	.00	.00
Single regimen	917	.42	.780	0	3	.00	.00	1.00
Combined regimen	167	.98	.960	0	3	.00	1.00	2.00
Infections								
Upper RTI	860					.00	.00	.00
Lower RTI	316	1.12	1.008	0	3	.00	1.00	2.00
Paranasal infections	50	.12	.435	0	2	.00	.00	.00
Upper Urinary Infections	65	.86	.882	0	3	.00	1.00	2.00
Lower Urinary Infections	195	.18	.504	0	3	.00	.00	.00
Diarrheal illness	178	.36	.693	0	3	.00	.00	.25
Intraabdominal infections	49	.71	.866	0	3	.00	.00	1.00
Genital infection	18	.33	.686	0	2	.00	.00	.25
Skin and soft tissue infection	111	.48	.784	0	3	.00	.00	1.00
Bone and Joint Infections	11	.55	.820	0	2	.00	.00	1.00
Endovascular infections	16	1.06	.854	0	2	.00	1.00	2.00
CNS Infections	9	1.22	.667	0	2	1.00	1.00	2.00
Abscess formation	19	.11	.315	0	1	.00	.00	.00
Eye İnfections	11	.00	.000	0	0	.00	.00	.00
Miscellaneous	49	.78	1.085	0	3	.00	.00	1.50
According to ultimate outcome								
Died	17	1.88	.697	0	3	2.00	2.00	2.00
Hospitalized in ICU	101	1.99	.781	0	3	1.00	2.00	3.00
Hospitalized in the ward	416	.99	.868	0	3	.00	1.00	2.00
Referred to another hospital	14	.64	.842	0	3	.00	.50	1.00
Refused hospitalization	3	.33	.577	0	1	.00	.00	.
Treated as outpatient	1406	.05	.245	0	2	.00	.00	.00

Presence of comorbid conditions									***P*-value**
Diabetes Mellitus	No	1669	.28	.655	0	3	.00	.00	.00	**0.0001**
	Yes	288	.91	.971	0	3	.00	1.00	2.00	
Chronic renal failure	No	1874	.34	.716	0	3	.00	.00	.00	**0.0001**
	Yes	83	1.16	.930	0	3	.00	1.00	2.00	
Acute renal failure	No	1899	.34	.713	0	3	.00	.00	.00	**0.0001**
	Yes	58	1.33	1.066	0	3	.00	1.00	2.00	
COPD	No	1776	.32	.697	0	3	.00	.00	.00	**0.0001**
	Yes	181	.87	.978	0	3	.00	1.00	2.00	
Cerebrovascular accident	No	1875	.32	.684	0	3	.00	.00	.00	**0.0001**
	Yes	82	1.62	.964	0	3	1.00	2.00	2.00	
Asplenia/ hyposplenism	No	1955	.37	.744	0	3	.00	.00	.00	0.301
	Yes	2	1.00	1.414	0	2	.00	1.00	–	
Congestive heart failure	No	1855	.33	.711	0	3	.00	.00	.00	**0.0001**
	Yes	102	1.07	.967	0	3	.00	1.00	2.00	
HIV infection	No	1954	.37	.745	0	3	.00	.00	.00	0.150
	Yes	3	.67	.577	0	1	.00	1.00	–	

RTI: Respiratory tract infections, CNS: Central nervous system infections, ICU: Intensive care Unit, COPD: Chronic obstructive pulmonary disease.

paradoxically more commonly in these countries compared to richer nations. In accordance with these consequences extended spectrum of antibiotics like third generation cephalosporins, carbapenems, and anti-Gram positive agents were used significantly more common in LMI countries. The probable reasons should be that the countries with limited resources have gaps in their infrastructures including sanitation, provision of clear water, and have less organized health care systems with limited access. Thus, infectious diseases make significant pressures on the healthcare systems as reflected in the EDs in this study. Presence of comorbid conditions and advanced age increased the severity of infections in EDs. BL/BLIs (15.7%), third-generation cephalosporins (12.8%), quinolones (10.5%), and macrolides (5.2%) were the most common antibiotics preferred in EDs. BLI/BLIs were most commonly used in upper RTI, paranasal, skin and soft tissue infections, and abscesses while respiratory quinolones in lower RTI, and older quinolones in diarrheal and lower urinary tract infections. Carbapenems, as one of the last resort antibiotics, were most commonly used in CNS and intraabdominal infections, in pyelonephritis, and in patients with sepsis. Anti-Gram-positive agents, probably due to widespread methicillin resistance in staphylococci,[14] were prescribed most often in endovascular infections in the EDs. Major break in the management chain seems that microbiological

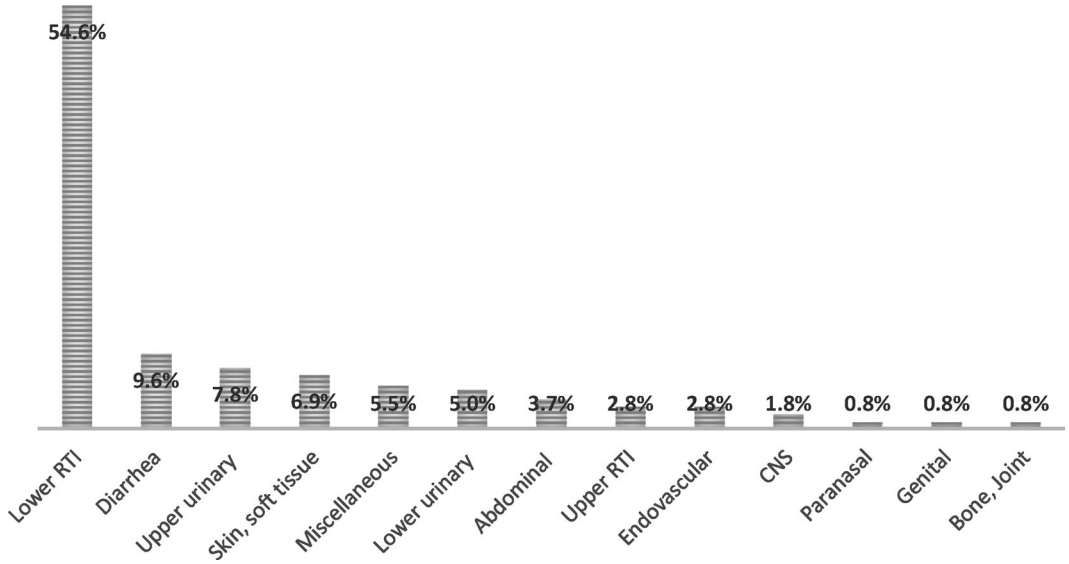

Figure 2. The distribution of patients with sepsis (qSOFA score ≥2). RTI: Respiratory tract infections, CNS: Central nervous system infections.

Table 5. The prevalences of infections in the emergency departments across the countries

	Total applicants to the EDs	Number of pts with infections	Prevalence (%)
Slovenia	39	37	94.87
Bosnia Herzegovina	36	22	61.11
Pakistan	54	31	57.41
Romania	48	27	56.25
Kazakhstan	115	56	48.70
United Arab Emirates	74	28	33.78
Albania	140	43	30.71
India	62	18	29.03
Croatia	139	32	23.02
Egypt	578	125	21.63
Bulgaria	26	5	19.23
Bangladesh	367	67	18.26
Turkey	6928	1141	16.47
Spain	456	73	16.01
France	223	34	15.25
Poland	176	25	14.20
Algeria	50	7	14.00
Bahrain	573	77	13.44
Slovak Republic	20	2	10.00
Israel	201	19	9.45
Saudi Arabia	295	26	8.81
Iran	280	22	7.86
Lebanon	54	4	7.41
Italy	623	36	5.78
TOTAL	11.557	1957	17.00

EDs: Emergency departments.

methods were not applied properly, and it appears that inappropriate decisions in hospitalizing patients may be likely.

In this study, antimicrobial drugs were given to one-tenth of all cases applied to EDs. Inappropriate antibiotic use can lead to adverse events, treatment failures, and drug resistance. Unfortunately, up to 40% of adults in the EDs were reported to face irrational use of antimicrobials.[15] According to our data, there were general trends to use relatively narrow spectrum antibiotics like penicillins, first and second-generation cephalosporins, BL/BLIs, and old quinolones or not to use carbapenems and anti-Gram-positive agents in mild cases. Likewise, single antibiotic regimens were mostly used in less severe cases compared to combination therapies. Accordingly, antimicrobials have been known to provide little benefit in patients with upper RTI.[16] However, although antibiotic overuse was noticeable in frequent BL/BLI prescriptions in upper RTIs, where penicillin derivatives without BLI would be adequate when antimicrobial therapy is indicated.[17] The probable reason may be the uncertainty of the ED physician for probable extension of infection to sinuses or to middle ear where beta-lactamase producing

microorganisms are common.[18] In addition, empirical use of carbapenems in the absence of antibiotic susceptibility data can be considered in the same context. In contrast, anti-Gram-positive agents were not combined to third-generation cephalosporins in the empirical treatment of acute bacterial meningitis[19,20] indicating lesser use. Hence, antimicrobial use still needs optimization in the EDs.

In this study, the mean qSOFA score was far low compared to sepsis threshold (qSOFA $\geq$2), and thus, we can say that although EDs provide whatever care is needed in routine practice, they basically served as outpatient clinics rather than providing care to critical patients. Accordingly, 44.8% of the cases were upper RTIs. According to our data, lower respiratory, upper urinary, endovascular, and CNS infections were the prominent infectious emergencies and thus, they should be managed as such in the EDs amongst the flow of none-critical patients. There are similar reports in the literature indicating pulmonary and urinary sources as the most common critical infections inside the ICUs.[21] In addition, we have shown that presence of comorbidities like diabetes, renal failure, COPD, cerebrovascular accident, and congestive heart failure have significantly increased the severity of infections in EDs indicating the need for multifaceted management strategies. As a strict example, COPD is usually interrelated to pneumonia and required frequent ICU admissions were already known.[22] Accordingly, we have shown that advanced age facilitated the development of sepsis in accordance with the literature.[23] Added to that, a visit to ED significantly increases the risk of acquiring new infections in the elders,[24] doubling the risk of adverse outcomes in this patient population.

Time is of essence in the treatment of sepsis, and early and aggressive treatment is central to decrease mortality. Thus, clinical judgement is a fast and reliable method to stratify between ICU and general ward admission in ED patients with sepsis.[25] In this study, although there was a general trend in the severity of the cases in descending order according to qSOFA scores for fatal patients, those hospitalized in the ICUs, and patients taken to the wards, 3.7% of the patients with sepsis ultimately were not hospitalized and were treated as outpatients. At this critical point, there seems to be problematic areas at initial patient assessment and hospital admission decisions, which should be better organized. In addition, there are serious concerns that key procedures for recognizing sepsis may be delayed[26] and the data of infecting pathogens are lacking[27] in ED patients. Accordingly, microbiological tests were applied only in 9.1% of ED patients in our study. As a concrete example, blood cultures, which is surely one of the mainstays of anti-infective management in critical patients were drawn merely in 10% of the patients with sepsis. This low rate may be explained by the fact that ED physician is forced to timely clinical diagnosis and microbiological tests are usually time consuming so that the ED physician has likely to left these details to the hospital department where the patient was ultimately taken. However, microbiological tests should not be neglected or delayed in life-threatening sepsis patients with the understanding that patient care is a continuous service and the data will be available out of ED in due course of hospitalization. Hence applying microbiological tests particularly in critical patients will contribute rational and timely management following the triage of the patients. Combined with the fact that antibiotics are started mostly in the EDs before the culture process, the expectations from the microbiology laboratory in curtailing therapy will become unrealistic. Given the fact that ED is an important patient supplier to ICU or one-fifth of the infections in the ICU belongs to community acquired origin,[28] microbiological diagnosis in the EDs is of paramount importance. Mortality in the ED is less than 1% in the single study day. However, it is crucial to emphasize both the mortality in community acquired infections can be quite significant[29,30] and the subsequent mortality in ICU patients will surely be noteworthy[19] indicating timely and proper management.

There were several limitations for this study. Since it was a single day point prevalence survey, the diagnosis was established with clinical and laboratory data other than microbiological tests in most cases. In addition, the long-term outcomes of the patients including mortality rates could not be provided. Finally, due to the heterogeneity of physicians' approaches on antibiotic allergy, we could not provide antibiotic modification decisions based on the history of antibiotic allergy. Our study showed that EDs commonly serve more as outpatient clinics, rather than serving critically ill patients. Microbiological diagnosis is infrequently applied, irrational antibiotic use and inappropriate decisions in hospitalizing patients seem possible. In countries with limited resources the infection patients tend to be more severely ill at presentation, and thus the infrastructures should be organized accordingly.

Authors' contribution

HE, SH, HA, HC, and JR conceived the study, designed the trial. HE supervised the conduct of

the trial and data collection. HE, HA undertook recruitment of participating centers and patients and managed the data, including quality control. SAC, ABK, MMK, MA, YYK, FK, JA, YC, AHMK, ID, EKDD, GAS, HH, AS, FL, ER, ML, HA, FKC, YR, DB, MJM AM, AM, AEK, DA, MSS, RK, SA, RED, EA, HMC, RB, DIM, BN, MEAD, ASSA, CRC, SRE, MWZ, OA, JZ, RES, NP, FA, IAD, SG, AAW, JEK, CBA, SK, MT, HPK, ND KK, AKK, MMP, AC, AL, RFD, LL, NM, JR collected data in their institutions in the study day, submitted datasets, contributed to data analysis, reviewed and revised the paper. HA provided statistical advice on study design and analyzed the data. HE, SH, SO, MJM drafted the manuscript, and all authors contributed substantially to its revision. HE, SH, JR takes responsibility for the paper as a whole.

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