

Intra-abdominal Infections: The Role of Anaerobes, Enterococci, Fungi, and Multidrug-Resistant Organisms

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Background. Intra-abdominal infections (IAI) constitute a common reason for hospitalization. However, there is lack of standardization in empiric management of (1) anaerobes, (2) enterococci, (3) fungi, and (4) multidrug-resistant organisms (MDRO). The recommendation is to institute empiric coverage for some of these organisms in “high-risk community-acquired” or in “healthcare-associated” infections (HCAI), but exact definitions are not provided.

Methods. Epidemiological study of IAI was conducted at Assaf Harofeh Medical Center (May–November 2013). Logistic and Cox regressions were used to analyze predictors and outcomes of IAI, respectively. The performances of established HCAI definitions to predict MDRO-IAI upon admission were calculated by receiver operating characteristic (ROC) curve analyses.

Results. After reviewing 8219 discharge notes, 253 consecutive patients were enrolled (43 [17%] children). There were 116 patients with appendicitis, 93 biliary infections, and 17 with diverticulitis. Cultures were obtained from 88 patients (35%), and 44 of them (50%) yielded a microbiologically confirmed IAI: 9% fungal, 11% enterococcal, 25% anaerobic, and 34% MDRO. Eighty percent of MDRO-IAIs were present upon admission, but the area under the ROC curve of predicting MDRO-IAI upon admission by the commonly used HCAI definitions were low (0.73 and 0.69). Independent predictors for MDRO-IAI were advanced age and active malignancy.

Conclusions. Multidrug-resistant organism-IAIs are common, and empiric broad-spectrum coverage is important among elderly patients with active malignancy, even if the infection onset was outside the hospital setting, regardless of current HCAI definitions. Outcomes analyses suggest that empiric regimens should routinely contain antianaerobes (except for biliary IAI); however, empiric antienterococcal or antifungals regimens are seldom needed.

Keywords. biliary infection; MDRO; epidemiology; nosocomial infections; surgical infection.

Intra-abdominal infections (IAI) constitute the primary diagnosis in 8% of hospitalizations [1], and they are the second most common infectious etiology associated with mortality in intensive care units [2]. However, IAI covers a broad spectrum of different syndromes, with diverse levels of severity, ie, from relatively simple and limited infections such as appendicitis to life-threatening complex infections that invade parenchymal organs and involve the peritoneal cavity [3, 4].

Several factors influence the outcomes of IAI, amongst them the delay in initiation of appropriate antimicrobial therapy (DAAT) [5, 6]. However, DAAT is frequent in IAIs [5–7]. Despite the establishment and distribution of treatment guidelines [3], there is still lack of standardization in empiric management, specifically for certain indications where DAAT is most common

[5–7]: ie, for anaerobes, fungi (almost exclusively *Candida* species), *Enterococcus* species (eg, *Enterococcus faecalis*, *Enterococcus faecium*), and multidrug-resistant organisms ([MDRO] eg, methicillin-resistant *Staphylococcus aureus* [MRSA], extended-spectrum β -lactamase [ESBL]-producing *Enterobacteriaceae*, and more) [8–13]. The aforementioned organisms are 4 groups of pathogens that may or may not be covered by empiric treatment regimens depending upon clinician discretion. Guidelines recommend institution of empiric coverage for these pathogens in “healthcare-associated infections” (HCAI), but the number of “high-risk” parameters required to support a definition for HCAI is not provided in these specific guidelines [3, 14].

There are various commonly used definitions for HCAI in the literature: the most commonly used are the “Duke-2002” [15] and the “modified Duke-2002” [16]. The Duke-2002 HCAI definition describes an infection that is present at hospital admission or within 48 hours of admission in patients that fulfilled any of the following criteria: (1) received intravenous therapy at home or wound care or specialized nursing care in the previous 30 days; (2) attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the previous 30 days; (3) hospitalized in an acute care hospital for ≥ 2 days in the previous 90 days; or (4) resided in a nursing home or long-term care facility. The modified Duke-2002

Received 5 May 2016; editorial decision 18 October 2016; accepted 30 October 2016.

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DOI: 10.1093/ofid/ofw232

definition simplified these criteria by altering the hospitalization criteria to ≥ 2 days in an acute-care hospital in the past year as the single criterion [17]. However, the performance of these definitions on an IAI cohort has not been measured or validated. Furthermore, IAI guidelines do not specifically provide treatment recommendations based on a particular HCAI definition [3].

There is an ongoing treatment decision conundrum between (1) initial prescribing of antibiotics targeting all possible causative pathogens and (2) strict adherence to antimicrobial stewardship guidelines to curb the continued emergence and spread of MDROs [18]. The aim of this study was to describe the epidemiology of IAIs and focus specifically on the role of anaerobes, fungi, enterococci, and MDROs in their causation. In addition, we tested the performances of the most established HCAI definitions [15, 16], to predict MDRO-IAI among our cohort of patients.

METHODS

Study Setting and Design

A retrospective study was conducted between July 2013 and October 2013 at Assaf Harofeh Medical Center ([AHMC] a referral university-affiliated 848-bed tertiary care facility), Israel. Assaf Harofeh Medical Center holds all services associated with IAI. Because the diagnostic coding system (eg, *International Classification of Diseases, Tenth Revision*) is neither sensitive nor specific enough to detect all IAIs [19], all discharge notes of patients who were admitted to AHMC during this entire period were reviewed by trained personnel. All patients (children and adults) with IAI (complicated and uncomplicated) per established criteria [3, 20] were included.

Possible IAIs included appendicitis, diverticulitis, infections of the biliary tract (eg, cholecystitis, cholangitis, “biliary pancreatitis”), colorectal infection (eg, epiploic appendagitis, typhlitis), and abdominal abscesses or peritonitis. All surgical-site infections [21], including deep organ space infections (with no evidence of infection of the surgical site itself), were excluded. Patients with gastroenteritis, *Clostridium difficile* infection, or other gastrointestinal luminal infections (eg, gastritis) were not included. The local institutional review board at AHMC approved the study before its initiation.

Data Collection

Data were extracted from patients’ hard copy and electronic charts and from microbiology and pharmacy records. These data included the following: patient demographics, comorbidities and past medical history, healthcare exposures, acute illness indices, microbiological data, and clinical outcomes. Mortality data were extracted from a national registry governed by the Israeli Ministry of Interior. Healthcare-associated infection was defined according to the Duke-2002 [15] and the modified Duke-2002 definitions [16], as previously mentioned.

Definition of Multidrug-Resistant Organisms and Microbiological Processing

For the purposes of this study, MDRO was defined as any one of the following: (1) MRSA; (2) ampicillin and/or vancomycin resistant enterococci; (3) *Enterobacteriaceae* nonsusceptible to 1 or more third-generation cephalosporins (eg, ceftriaxone, ceftazidime, cefotaxime—this marker led to inclusion of isolates expressing various broad-spectrum β -lactamases including ESBLs (ie, bla_{CTX-M} , bla_{SHV} , bla_{TEM} , bla_{AmpC} and various carbapenemases (eg, bla_{KPC} , bla_{NDM}) in a sensitivity and specificity of over 99% based on preliminary pilot analysis [22]; (4) *Pseudomonas aeruginosa*; and (5) *Acinetobacter baumannii*. These pathogens were chosen after a review of pathogens from 2011 to 2012, managed by the Infectious Diseases unit, which were not susceptible to the initial prescribed antibiotic regimen, based on the hospital’s IAI treatment guidelines, which resembles the practice guidelines of the Infectious Diseases Society of America [23]. Vitek-2 (bioMerieux, Marcy l’Etoile, France) was the automated system in use at AHMC throughout the study period, to determine pathogens’ identification and their susceptibilities to various agents. Appropriate antimicrobial therapy was defined based on the in vitro susceptibilities of the pathogen, as distributed by the Microbiology laboratory’s formal report.

There are uniform standards for obtaining microbiological cultures at AHMC. As per established criteria [3], blood cultures are always obtained from complicated and/or nosocomial IAI, and both aerobic and anaerobic bottles are filled with 10–20 mL of blood. For cultures obtained at the operating room or radiology services, the practitioners are instructed to fill the sample in either blood cultures bottles (always fill both aerobic and anaerobic bottles) or in sterile packages, which is usually the same package being used to transport urine cultures. When sample is obtained through a sterile package, it is not being transported nor processed in anaerobic conditions.

Statistical Analysis

The descriptive epidemiology, along with risk factors and outcomes analyses (for anaerobic, fungal, enterococcal, and MDRO infections), were analyzed by logistic and Cox regressions, respectively. The HCAI definitions performances in predicting MDRO-IAI upon hospital admission were analyzed by calculating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the receiver operating characteristic curve (AUC ROC), for each of the HCAI definitions.

RESULTS

A total of 8129 patients were hospitalized at AHMC during the study period. The discharge summaries of all patients were carefully reviewed, and 253 patients met the inclusion criteria for IAI and were included in the study (Figure 1): 92 patients (36%) had complicated infection per definition [3], 137 (54%) were males, and 43 (17%) were children under 18 years of age.

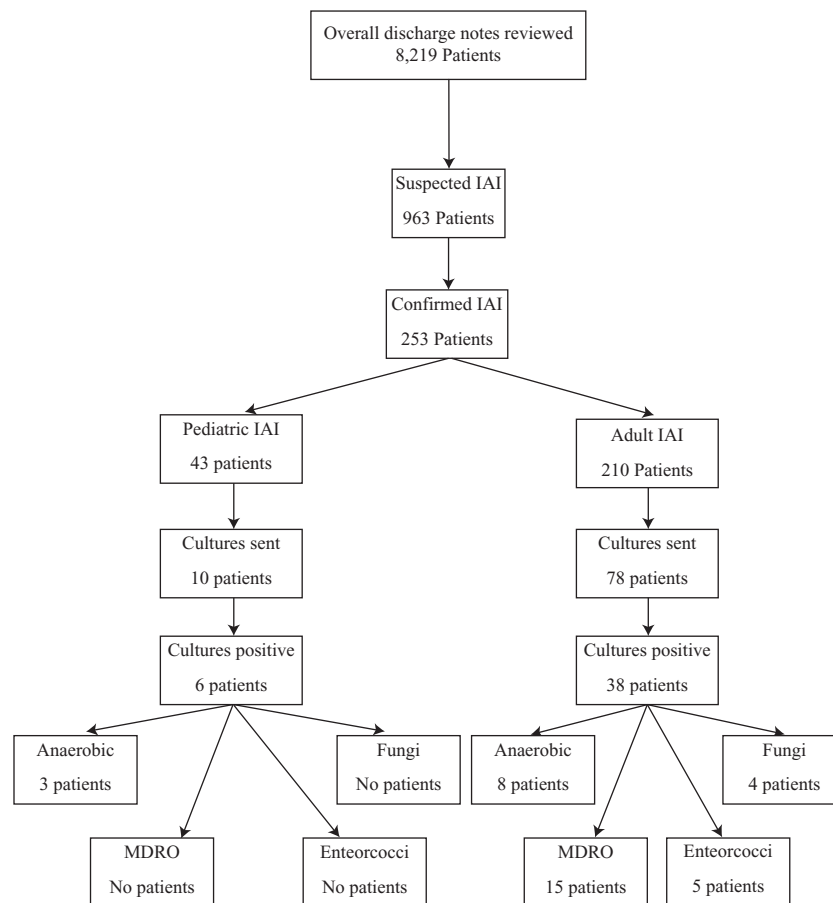


Figure 1. A flow chart of patients with intra-abdominal infections (IAI), Assaf Harofeh Medical Center (May to November, 2013). Abbreviation: MDRO, multidrug-resistant organisms.

None of the patients were neonates. There were 116 patients with appendicitis, 93 had infections associated with the biliary tree, 17 had diverticulitis, 14 had abdominal abscess/abscesses, 8 had peritonitis, and 5 had colorectal infections. All but 3 IAIs (1.2%) were initiated outside of acute-care hospital settings (ie, community-onset infections). Selected epidemiological features, for the main IAI syndromes, are depicted in [Table 1](#).

Cultures were obtained from 88 patients (35%), and 44 of them (50%) yielded a microbiologically confirmed diagnosis ([Figure 1](#)). The most common pathogen was *Escherichia coli* (25%), followed by *P aeruginosa* (10.4%) and *Bacteroides fragilis* (9.1%). Nineteen patients (22%) had polymicrobial infection. The subanalyses of epidemiological features associated with specific pathogens were conducted among the 44 patients with microbiologically confirmed infection.

Anaerobic Intra-abdominal Infections

There were 11 patients with anaerobic IAI: 5 with appendicitis, 2 with peritonitis, 2 with abdominal abscess, 1 with diverticulitis, and 1 had colorectal infection. None had biliary or biliary-associated IAI. Three (27%) of the anaerobic IAI were among children. *Bacteroides fragilis* was the causative pathogen

in 7 patients, followed by *Prevotella oralis* (n = 5), *Bacteroides thetaiotaomicron* (n = 4), *Bacteroides ovatus* (n = 2), *Bacteroides distasonis* (n = 1), and *Prevotella bivia* (n = 1). In 6 patients, more than 1 anaerobic pathogen was recovered. In univariable analysis of adult patients with anaerobic IAI (n = 8) versus patients with nonanaerobic IAI (n = 30), patients with anaerobic IAI were significantly younger (52 ± 22 vs 68 ± 14 years, $P = .02$), often with polymicrobial infection (88% vs 27%, $P = .003$). Appendicitis was significantly associated with anaerobic IAI (odds ratio [OR] = 8.4, $P = .02$).

Therapeutic management data were available for 10 of the 11 patients (both adults and pediatrics). Nine patients were treated empirically with an appropriate antianaerobic agent. Two patients (ie, 18%) with anaerobic IAI died during hospitalization: one with advanced colon cancer and massive secondary peritonitis (due to *B fragilis*), and the second was an elderly individual who presented with spontaneous bacterial peritonitis due to *E coli* and *P oralis*. Both patients received an appropriate empiric regimen. Among the adult survivors of anaerobic IAI (n = 6), the median length of stay from infection to discharge was 13 days (range, 6–21), 3 (50%) had additional hospitalizations attributed to the index IAI, 3 (50%) had

Table 1. Epidemiological Characteristics of Patients With Intra-abdominal Infection, Assaf Harofeh Medical Center (July–October 2013)

Parameters	Cohort N (Valid %) ^a	Diverticulitis N (Valid %) ^a	Appendicitis N (Valid %) ^a	Biliary N (Valid %) ^a
Total	253	17	116	93
Demographics				
Age, years, mean ± SD	46.3 ± 25.1	65 ± 11.5	27.3 ± 17.7	63.1 ± 19.2
Male gender	137 (54.4)	11 (64.7)	71 (61.2)	39 (41.9)
Age group				
0–3 months	0	0	0	0
3 months–5 years	3 (1.2)	0	3 (2.6)	0
5–17 years	40 (15.9)	0	38 (32.8)	2 (2.2)
18–64 years	135 (53.6)	9 (52.9)	70 (60.3)	40 (43)
Over 65 years	74 (29.4)	8 (47.1)	5 (4.3)	51 (54.8)
Background conditions				
BMI, mean ± SD or median (range)	27 ± 6.3	29.7 (25.2–32.8)	23.4 (12.6–40.1)	29.6 ± 6.1
Smoking	63 (24.9)	7 (41.2)	18 (15.5)	28 (30.1)
Ischemic heart disease	27 (10.7)	4 (23.5)	3 (2.6)	13 (14)
Dependent functional status	40 (15.8)	4 (23.5)	1 (0.9)	29 (31.2)
Dementia	11 (4.3)	0	0	10 (10.8)
Malignancy (past or active)	22 (8.7)	1 (5.9)	0	14 (15.1)
Charlson's combined condition score [30], median (range) or mean ± SD	0.8 (0–12)	2.8 (0–10)	0.1 (0–7)	3.8 ± 3
Immunosuppression ^b	8 (3.2)	0	0	3 (4.2)
Permanent device ^c	16 (6.3)	1 (5.9)	0	10 (10.9)
Recent invasive procedure ^d	35 (13.8)	3 (17.6)	1 (0.9)	20 (21.5)
Previous IAI (past 6 months)	49 (19.4)	1 (5.9)	7 (6)	33 (35.5)
Acute illness characteristics and indices				
Location of infection acquisition				
Community onset	238 (94)	16 (94.1)	114 (98.3)	89 (95.7)
Hospital acquired	15 (5.9)	1 (5.9)	2 (1.7)	4 (4.3)
Necessitated ICU hospitalization	4 (1.6)	1 (5.9)	0	3 (3.2)
Severe level of sepsis ^e	15 (6)	1 (5.9)	0	6 (6.5)
Serum albumin (g/L), mean ± SD	33.1 ± 5.7	35.7 ± 5.2	33.5 ± 4.8	33.5 ± 5.4
Invasive procedure performed during acute illness	170 (68.8)	3 (17.6)	99 (85.3)	51 (56.7)
Microbiology parameters				
Cultures obtained during acute infection	88 (34.8)	6 (35.3)	21 (18.1)	40 (43)
Polymicrobial infection	19 (22)	1 (16.7)	7 (35)	2 (5)
MDRO ^f	15 (17)	2 (33.3)	0	7 (17.5)
Anaerobe	11 (12.5)	1 (16.7)	5 (23.8)	0
<i>Enterococcus</i> species	5 (5.7)	0	2 (9.5)	2 (5)
Fungi	4 (4.5)	0	0	2 (5)
Recent MDRO ^f carriage (in the previous 3 months)	15 (17)	1 (5.9)	0	1 (1.1)
Antimicrobial parameters				
Exposure to antibiotics in the previous 3 months	66 (26.1)	5 (29.4)	12 (10.3)	35 (37.6)
Time to appropriate antibiotics, days, median (range)	0 (0–20)	0	0	1 (0–13)
Clinical outcomes				
Mortality				
In-hospital	13 (5.1)	1 (5.9)	0	8 (8.6)
14 days	10 (4)	0	0	7 (7.5)
3 months	16 (6.3)	1 (5.9)	0	11 (12)
Length of hospitalization from infection to discharge, excluding deceased, days, median (range)	4 (1–65)	4.5 (1–7)	2.7 (1–22)	4.8 (1–65)
Functional status deterioration [24]	12 (5)	1 (6.3)	0	7 (8.1)
Discharge to LTCF after being admitted from home	12 (5)	0	0	10 (11.8)
Additional hospitalization within 6 months				
Overall	67 (27.9)	3 (18.8)	19 (16.5)	38 (44.2)
Attributable to index IAI	60 (25.3)	2 (12.5)	15 (13.3)	37 (43)

Abbreviations: BMI, body mass index; CRE, carbapenem-resistant *Enterobacteriaceae*; HIV, human immunodeficiency virus; IAI, intra-abdominal infection; ICU, intensive care unit; LTCF, long-term care facility; MDRO, multidrug-resistant organisms; SD, standard deviation; TNF, tumor necrosis factor.

^aValid percentages designate the percentage after deducting missing values from the denominators.

^bAny one of the following: (1) neutropenia (<500 neutrophils/cell³); (2) glucocorticoid use (mean daily dose equivalent to 16 mg of prednisone, given for at least 5 days) in the past month; (3) chemotherapy in the past 3 months; (4) radiotherapy in the past 3 months; (5) HIV; (6) any transplantation; or (7) anti-TNF- α therapy in the past 3 months.

^cTracheotomies, tunneled central lines, silicon-based urinary catheters, orthopedic external fixators, implanted defibrillator, pacemaker, drains of any type. Excluding heart valves or joint replacements, or any internal stents.

^dAny type of surgery, endoscopy, permanent central line insertions, or percutaneous procedure in the past 6 months.

^ePer established definition [31].

^fMDRO includes any one of the following isolates: (1) methicillin-resistant *Staphylococcus aureus* (MRSA), (2) ampicillin- and/or vancomycin-resistant enterococci, (3) penicillin-resistant *Streptococcus pneumoniae*, (4) *Acinetobacter baumannii*, (5) *Pseudomonas aeruginosa*, (6) any *Enterobacteriaceae* resistant to any third- or fourth-generation cephalosporin, (7) any *Enterobacteriaceae* resistant to any carbapenem (CRE).

experienced permanent deterioration in their functional status [24], and 3 (50%) were discharged to a long-term facility after being admitted to the index hospitalization from home. Although all of these clinical outcomes were worse among the cohort of patients with anaerobic IAI, none of these associations were statistically significant.

Fungal Intra-abdominal Infections

There were only 4 patients (1.6% of the entire cohort and 9% of those with microbiologically confirmed IAI) with fungal IAI. All infections were among adults, and all were polymicrobial. Two patients had a biliary-originating IAI, and 2 presented with peritonitis after gastrointestinal endoscopy. One of the isolates was *Candida albicans* and the others were non-*albicans* *Candida* species. All of the patients with fungal IAI were males ($P = .1$). An antifungal agent was administered empirically to only 1 patient, who presented with peritonitis after gastroscopy was conducted in an ambulatory clinic. In univariable analysis, the only epidemiological feature significantly associated with fungal IAI was the significant delay in initiation of appropriate therapy (median of 4 days [range, 0–13] among those with fungal IAI vs 0 days [median 0–18] among patients with non-fungal IAI; $P = .03$). Despite the fact that appropriate treatment was delayed, none of the patients died in-hospital. However, patients with fungal IAI suffered more often from permanent deterioration in their functional status per Katz criteria [24] (OR = 18, $P = .01$) and from prolonged length of stay from infection to discharge (14 days [range, 11–42] vs 7 days [range, 1–36]; $P = .01$).

Enterococcal Intra-abdominal Infections

There were 5 patients (all adults) with enterococcal IAI (3 *E faecium*, 1 *Enterococcus gallinarum*, and 1 *Enterococcus avium*): 2 had appendicitis, 2 had biliary-originating IAI, and 1 had an intra-abdominal abscess. All patients were male ($P = .06$). Three patients (60%) had polymicrobial-confirmed IAI. No significant predictors were associated with enterococcal IAI versus nonenterococcal microbiologically confirmed IAI ($n = 39$). Empiric therapy active against enterococci was administered to 4 patients (80%). None of the patients died, and enterococcal IAI was not associated with any additional worse outcome.

Intra-abdominal Infections Caused by Multidrug-Resistant Organisms

Overall, there were 15 patients with IAI caused by an MDRO (34% of patients with microbiologically confirmed IAI): 8 with *P aeruginosa*, 6 with ESBL-producing *Enterobacteriaceae*, 1 with MRSA, and 1 with *A baumannii*. All patients with MDRO-IAI were adults. Seven patients had a biliary infection, 3 presented with peritonitis, 3 with intra-abdominal abscesses, and 2 with diverticulitis. In univariable analysis, patients with MDRO were significantly older (70 ± 12 vs 50 ± 28 years, $P = .002$), dependent in terms of their background functional status (OR = 4.2, $P = .04$) [24], with higher Charlson's combined condition score ($P = .009$) and more often with active malignancy (OR = 6.8,

$P = .04$). In terms of acute illness indices, patients with MDRO presented more often with reduced cognition (OR = 5.5, $P = .03$). In multivariable analysis, the independent risk factors for MDRO-IAI remained advanced age (OR = 1.04, $P = .04$) and active malignancy (OR = 5.6, $P = .05$). Patients with MDRO-IAI suffered more from (1) delay in initiation of active therapy of more than 48 hours (OR = 6.7, $P = .04$), (2) 90-day mortality rate (OR = 9, $P = .01$), and (3) prolonged length of stay from infection to discharge (after excluding the patients who died; $P = .007$).

The Performances of Current Definitions of Healthcare-Associated Infections to Predict Multidrug-Resistant Organisms Intra-abdominal Infections

Two hundred fifty (99%) IAIs were initiated outside of the acute-care hospital setting (ie, "community-onset"): 191 were community-acquired and 50 were HCA based on the Duke-2002 criteria [15]. For 9 patients, possible exposures per Duke-2002 could not be ascertained. Among the microbiologically confirmed community-onset cases ($n = 41$), 15 were HCA per Duke-2002 (38% of those with available data), and, among them, 8 (53%) were MDROs. We tested the performances of the Duke-2002 HCA definition in predicting MDRO among patients with community-onset IAIs: the sensitivity was 64%, specificity was 83%, PPV was 64%, NPV was 83%, and the AUC ROC was 0.73. When we tested the performances of the modified Duke-2002 definition [16], the sensitivity was 64%, specificity was 75%, PPV was 54%, NPV was 82%, and AUC ROC was 0.69.

DISCUSSION

Intra-abdominal infection is a common infection with variable possible pathologies and potentially serious complications and outcomes. Despite official guidelines [3], there is a lack of evidence from controlled trials pertaining to empiric coverage for *Enterococcus*, fungi, anaerobes, and MDROs. One of the reasons for the lack of standardization is that no exact definitions are provided. In this study, 253 consecutive patients with IAI were enrolled, while meticulously avoiding selection bias commonly associated with computerized diagnostic coding [19]. Approximately 17% were children, with the vast majority of them suffering from acute appendicitis.

According to our analyses, empiric enterococcal coverage is seldom needed [3]. These isolates were recovered only from 11% of microbiologically confirmed IAI (5 patients), and the outcomes associated with these infections were not worse compared with the other infections, even when active treatment was delayed (ie, for 72 hours, until culture results became available). Guidelines do not recommend routine usage of enterococcal coverage, at least not for "community-acquired" IAI [3]. Moreover, *Enterococcus* was only 1 of several pathogens isolated in 60% of the patients, and it is debatable whether enterococcal coverage should be instituted in those circumstances [3].

The incidence of fungal infections (all *Candida* spp, all polymicrobial infections) was even lower (9% of microbiologically confirmed IAI, n = 4). Official guidelines recommend complete avoidance of antifungals for community-acquired infections, although according to our analysis, despite the small sample size, in patients presenting with IAI after a gastrointestinal endoscopic procedure, it is reasonable to consider the empiric usage of antifungals, even though *Candida* was only one of the isolated pathogens in all patients (100%). One can argue that peritonitis after an endoscopic procedure, even if conducted in ambulatory setting, is a “healthcare-associated” event per guidelines and not a community-acquired event. However, this differentiation between definitions is not depicted clearly in the guidelines [3]. Of note, 3 of 4 patients were diagnosed with non-*albicans* *Candida* species, and in 2 of 4 patients the *Candida* was non-susceptible to fluconazole, which is the most commonly used empiric antifungal agent [3]. Indeed, patients with fungal IAI in our cohort suffered from significant delays in initiation of active therapy and from significantly worse morbidity (but not mortality) outcomes. A detailed and much larger analysis of fungal IAI is warranted, with controlled analyses of independent predictors and outcomes. Such investigation could guide the appropriate empiric management of fungal IAI, stratified by the exact clinical syndrome and/or scenario, since the epidemiology of fungal IAI evolved considerably in the past years [17, 25, 26].

According to this analysis, it seems that anaerobic empiric coverage is indeed an appropriate practice in many IAIs. Despite probable underdiagnosis due to suboptimal transport and/or processing anaerobic conditions (particularly for samples obtained at the operating room), there were still 25% (n = 11) of patients with anaerobic-confirmed IAI. The outcomes of patients with anaerobic IAI were worse, although the majority had received appropriate early antibiotics. This again highlights the importance of instituting early antianaerobic coverage for every IAI, regardless of the exact IAI type, except in biliary-originated IAI [3]. In our analysis, none of the biliary IAIs were caused by anaerobic pathogens, which justify this practice.

As been clearly demonstrated in many other recent reports, MDROs (particularly *P aeruginosa*, ESBLs, and MRSA) should be suspected even in community-onset IAI [10, 27–29]. According to our analyses, empiric coverage of MDRO is specifically important and justified among the elderly with an active malignancy. Patients with MDRO-IAI have been shown to suffer from worse outcomes, including a significant association with increased 90-day mortality rate [3]. The guidelines again (such as in the case of fungal and enterococcal infections) suggest considering MDRO only in HCA infection (with no exact definition provided), based on the local epidemiology [3]. In our analysis, 80% of MDRO IAIs were among patients

with community-onset (not necessarily community-acquired) infection. When we tested the performances of the most established and widely used HCA infection definition, the Duke-2002 [15], to predict the likelihood of MDRO infection, the performances were relatively low with ROC AUC of only 0.73. We tested the performances of an additional widely used definition, the modified Duke-2002 [16], and performances were even lower (ROC AUC 0.69). This implies that current guidelines do not assist clinicians in anti-MDRO empiric coverage, particularly because an HCA definition is not provided in the guidelines [3]. A validated analysis to predict MDRO-IAI among patients with community-onset infection, upon admission to an acute-care hospital, is definitely warranted, to guide clinicians on this important and common matter. A validated HCA definition, with higher performances in predicting MDRO, could improve patients’ outcomes (by reducing the frequent delays in initiation of appropriate therapy), while avoiding broad-spectrum (and sometimes toxic) therapeutics administered to the “wrong population”, ie, patients with IAI caused by susceptible pathogens. It is important to note that current guidelines also do not differentiate nosocomial IAI from community-onset HCA IAI. It is obvious per guidelines that nosocomial IAI are HCA and therefore MDRO coverage should be considered (based on local epidemiology) [3]. Indeed, all 3 microbiologically confirmed nosocomial IAIs in our cohort were caused by an MDRO.

Our study suffers from several obvious limitations. Its retrospective chart review-based design imposes possible confounders associated with availability and accuracy of the captured data. In addition, IAI is a very broad clinical entity, composed of various “different diseases”, depending on age (eg, adults vs pediatrics) and the exact clinical syndrome (eg, appendicitis vs diverticulitis). By stratifying our cohort of over all 253 patients, we were underpowered to conduct additional subanalyses that could have potentially strengthened our findings. In addition, it is a single-center analysis, and geographical differences in carriage of organisms and regional susceptibility patterns could alter its conclusions.

CONCLUSIONS

We conducted detailed epidemiological analyses on a cohort of 253 patients with a variety of IAIs, focusing specifically on few knowledge gaps in terms of therapeutic management of IAI among hospitalized patients. We believe that our analyses show, although limited by small sample size, that further analyses pertaining to the therapeutic management of fungal IAI among adults are needed. In addition, MDROs are becoming common causative agents of IAI, particularly among adults. Patients with MDRO-IAI suffer from significant delays in initiation of appropriate antibiotics and from significantly worse outcomes, including mortality. Current guidelines are unclear as to when to institute empiric coverage for MDROs, and our analyses also

prove that currently used definitions do not effectively direct the management of these infections. A clear definition for HCAI and clear recommendations for empiric MDRO coverage are needed, to improve patients' outcomes, particularly among the elderly.

Acknowledgments

This work was performed by Samuel Levy in partial fulfillment of the MD thesis requirements of the Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel.

Disclaimer. MSD-Israel had no access or involvement in data collection and data interpretation and was not involved in the process of drafting this manuscript. The company also did not review nor had any access to the manuscript prior to its publication.

Financial support. This study was funded in part by MSD-Israel.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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