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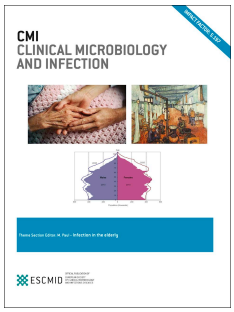

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Incidence of co-infections and superinfections in hospitalised patients with COVID-19: a retrospective cohort study

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Key words: COVID-19; co-infections; superinfections; mortality.

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ABSTRACT

Objectives: We aimed to describe the burden, epidemiology and outcomes of co-infections and superinfections occurring in hospitalised patients with COVID-19.

Methods: Observational cohort study of all consecutive patients admitted ≥ 48 hours to Hospital Clinic of Barcelona for COVID-19 (February 28th - April 22nd, 2020) who are currently discharged or dead. We describe demographic, epidemiologic, laboratory, and microbiologic results, as well as outcome data retrieved from electronic health records.

Results: Of a total of 989 consecutive patients with COVID-19, 72 (7.2%) had 88 other microbiologically confirmed infections: 74, bacterial; 7, fungal and 7, viral. Community-acquired co-infection at COVID-19 diagnosis was uncommon (31 out of 989, 3.1%) and mainly caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*. A total of 51 hospital-acquired bacterial superinfections, mostly caused by *Pseudomonas aeruginosa* and *Escherichia coli*, were diagnosed in 43 (4.7%) patients, with a mean time from hospital admission to superinfection diagnosis of 10.6 (SD 6.6) days. Overall mortality was 9.8% (97/989). Patients with community-acquired co-infections and hospital-acquired superinfections presented with worse outcomes.

Conclusions: Co-infection at COVID-19 diagnosis is uncommon. Few patients developed superinfections during hospitalisation. These findings are quite differential when compared with those of other viral pandemics. As it relates to hospitalised patients with COVID-19, such findings could prove essential in defining the role of empiric antimicrobial therapy or stewardship strategies.

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has presented a formidable medical challenge before health systems and clinicians [1–4]. With >250,000 cases diagnosed by 9 July, Spain has particularly suffered from this pandemic [5]. Many decisions have been made with limited clinical experience and scientific evidence, especially as it concerns treatments for patients hospitalised with the coronavirus disease 2019 (COVID-19). One such clinical decision is that regarding the use of antibiotic therapy in patients with COVID-19. Bacterial, especially *Streptococcus pneumoniae* and *Staphylococcus aureus*, and viral or fungal co-infections are common complications described as arising in other pandemics caused by *influenza* viruses [6–9]; however, information concerning incidence of such co-infections in patients with COVID-19 has been scarce. Similarly, information related to COVID-19 superinfections is lacking, although it is essential to rational antimicrobial stewardship.

We aimed to describe the burden and epidemiology of community-acquired co-infections and hospital-acquired superinfections in a large cohort of all consecutive hospitalised patients admitted with COVID-19 for 48 hours or more in Barcelona, who are either currently discharged or dead. The impact of co-infections and superinfections on patient outcomes was also described.

METHODS

Study design and patients

This observational cohort study was performed at Hospital Clinic in Barcelona (Spain), a 700-bed university centre that provides broad and specialised medical, surgical, and intensive care for an urban population of 500,000 adults (>18 years old). All patients admitted with COVID-19 for ≥48 hours between 28 February and 22 April 2020, and who are currently discharged alive or had died during hospitalisation, were included. All patients had a diagnosis of COVID-19 confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) testing performed on nasopharyngeal throat swab specimens, and/or by fulfilling clinical diagnostic criteria provided during the pandemic peak for SARS-CoV-2. These criteria comprised the presence of any of the following respiratory symptoms, including sore throat, congestion, cough, dyspnoea, new loss of taste and/or smell, as well as uni- or bilateral interstitial infiltrates in the chest X-ray. The Institutional Ethics Committee of Hospital Clinic of Barcelona approved the study and due to the nature of the retrospective data review, waived the need for informed consent from individual patients (HCB/2020/0273).

Data collection and outcomes

For all patients hospitalised with COVID-19, data concerning demographics (age, gender), epidemiology, comorbidities, laboratory tests, microbiological results (blood and urine cultures, respiratory samples, urinary antigen tests and antimicrobial susceptibility), treatment and outcomes (intensive care unit [ICU] admission, length of hospital stay, and mortality) were collected directly from electronic health records (EHR) as previously described [10]. The EHR of all patients with positive microbiologic

results were reviewed by one of our researchers (CGV, EMG or CC) to assess clinical significance.

Procedures

Investigation of bacterial, viral and fungal pathogens in blood, normally sterile fluids, sputum and other samples was performed with standard microbiologic procedures upon hospital admission, as requested by the attending physician. Bacterial respiratory infection was diagnosed in patients with 1 or more positive cultures of respiratory pathogens obtained from blood, pleural fluids, good-quality sputum (>25 polymorphonuclear leukocytes and <25 epithelial cells) and bronchoalveolar lavage, and/or a positive urinary antigen test. *S. pneumoniae* antigen in urine was detected with a rapid STANDARD F *S. pneumoniae* Ag FIA assay (SD Biosensor, Inc. Republic of Korea). Specific, rapid RT-PCR testing was used for *influenza* A and B viruses, as well as respiratory syncytial virus (RSV) diagnosis (cobas Liat System, Roche). Multiplex PCR testing (Flow System, Roche) was also used for *influenza* viruses: A, B and C; *parainfluenza*: 1,2,3 and 4; and metapneumovirus diagnosis.

Definitions

Bloodstream infection (BSI) was defined as the growth of a non-skin flora commensal from ≥ 1 blood culture. To define a BSI as that caused by a common skin coloniser such as coagulase-negative staphylococci or *Corynebacterium*, we required ≥2 blood cultures drawn from different sites and a clinical evaluation from one of our researchers (CGV or EMG). We then considered the clinical significance of such BSI. Urinary infection was defined as the growth of a bacterium or fungus in a urine culture

from a patient with clinical symptoms and/or the consideration of such urinary infection as clinically significant by one of our researchers (CGV or EMG). *Aspergillus* tracheobronchitis was defined as the isolation of *Aspergillus* species from endobronchial specimens of intubated patients with purulent secretions, as well as clinical validation from one of our researchers (CGV or CC).

All of these clinically-indicated infections were categorised as co-infections or superinfections. If diagnosis was at onset or within the first 24h of COVID-19 hospital admission, these infections were defined as community-acquired co-infections. If diagnosis occurred ≥48h of admission for COVID-19, these infections were defined as hospital-acquired superinfections.

Statistical analysis

For the purpose of the present study, a descriptive analysis of clinical and laboratory tests was performed. Continuous and categorical variables were presented as median (interquartile range [IQR]) and absolute number (percentage), respectively. We used the Mann-Whitney U-test, $\chi 2$ test and Fisher's exact test to compare differences between patients who had other infections and those who did not. Significance was a p-value <0.05. Statistical analyses were performed with Microsoft SPSS-PC+, version 22.0 (SPSS, Chicago, IL, USA).

RESULTS

We assessed 989 consecutive adults with COVID-19 at our hospital who had either been discharged or had died during the study period. Of these, 552 (55.8%) were male and the median age was 62 (IQR 48-74) years. Main patient characteristics by groups are shown in Table 1. Table 2 details the number of microbiology tests requested by attending physicians and positive results with clinical significance. A total of 88 non-COVID-19 infections were documented in 72 (7.3%) patients: 74, bacterial; 7, fungal; and 7, viral. A total of 74 bacterial infections were diagnosed in 61 of 88 patients (3 infections in one patient, 2 in 12 individual patients and 1 in every remaining patient). The most common bacteria isolated were *S. pneumoniae (12 cases); S. aureus, 12*; *Pseudomonas aeruginosa, 10*; *Escherichia coli, 7*; and *Klebsiella pneumoniae, 6*.

Community-acquired co-infections

Overall, 31 of 989 (3.1%) patients had 37 community-acquired co-infections. Thirty community-acquired bacterial co-infections were documented in 25 (2.5%) patients. Specifically, bacterial pneumonia co-infection was documented in 21 (2.1%) patients at COVID-19 diagnosis. Two of these co-infections were with different bacteria. *S. pneumoniae* (one patient had a *Moraxella catarrhalis* co-infection) and *S. aureus* (one patient had a *Haemophilus influenzae* co-infection) were the most common bacteria in this scenario. Two patients had infections caused by methicillin-resistant *S. aureus*. Diagnosis of community-acquired bacterial co-infection was performed with one or more of the following tests: urinary antigen test in 12 cases; good quality sputum, 2 and blood cultures, 1.

Viral community-acquired co-infection was detected in 7 of 989 (0.6%) patients, of whom one presented with bacterial co-infection as well: 4 cases of *influenza A* virus co-infection; 1, *influenza B* virus; 1, respiratory syncytial virus and 1, herpetic disease. Two of these 7 (28.6%) patients, with *influenza A* and *influenza B* virus co-infections, respectively, died.

Hospital-acquired superinfections

A total of 51 hospital-acquired superinfections were documented in 43 patients. Of these, 44 were bacterial and diagnosed in 38 (3.8%) patients. The mean time from hospital admission to superinfection diagnosis was 10.6 (SD 6.6) days. Of these 44 superinfections, 25 (56.8%) occurred in patients admitted to the ICU. The most frequently isolated microorganisms were *P. aeruginosa* (8 cases); *E. coli, 6; Klebsiella* spp.*, 5* and *S. aureus, 5*. The most common hospital-acquired superinfections were those of the respiratory tract and bacteremia. Multidrug-resistant Gram-negative bacteria (MDR-GNB) were isolated in 7 patients: 3, MDR-*P. aeruginosa* infection; 2, Extended-Spectrum ß-Lactamase (ESBL)-*E. coli*; and 2, ESBL-*K. pneumoniae*. Table 3 details epidemiology of all bacterial co-infections and superinfections.

Seven of 989 (0.7%) patients had fungal hospital-acquired superinfections: 3 cases caused by *Aspergillus fumigatus* and 4, *Candida albicans.* Two patients were diagnosed with bacterial and fungal superinfections. All three patients with tracheobronchitis caused by *A. fumigatus* had prior lung disease and a median age of 75 (IQR 70-75) years. These patients were also critically ill and received mechanical ventilation support and high corticosteroid dosage. In this series of patients, only one died. Patients with *C. albicans* superinfection had the following clinical syndromes: two

cases of candidemia in an ICU setting; one case of a nosocomial urinary tract infection related to a urinary catheter and one case of a complicated intra-abdominal infection. Two patients died.

Outcomes

Overall mortality for patients hospitalised with COVID-19 for 48 hours or more was 9.8% (97 of 989 patients). Table 1 details the most important outcomes in hospitalised patients with COVID-19 who present without infection, those with community-acquired co-infection and those with hospital-acquired superinfection. Remarkably, patients with community-acquired co-infections were admitted to the ICU more frequently. In comparison to those without infection, patients with hospital-acquired superinfections had prolonged length of hospital stay and higher mortality.

DISCUSSION

We present a large series of patients from a Spanish region dramatically affected by the COVID-19 pandemic, focusing on describing community-acquired co-infections and hospital-acquired superinfections in these patients. Remarkably, bacterial pneumonia co-infection in patients hospitalised for COVID-19 was lower when compared with co-infections occurring in patients suffering from other respiratory virus infections such as *influenza* H1N1 or *influenza* H3N2 [6,8,11,12]. A minority of patients had bacterial or fungal superinfections and co-infections caused by other viruses.

Our results are concordant with a recent review that summarised nine studies reporting data concerning co-infections in patients with COVID-19. An 8% rate for bacterial and fungal co-infections was described [13]. In a recent letter, Kim et al reported relatively low rates (ranging from 0% for most pathogens to 12% in rhinovirus/enterovirus) of co-infections between SARS-CoV-2 and other respiratory pathogens [14]. Bacterial community-acquired pneumonia co-infections documented in our cohort have been especially low. Considering the high number and severity of bacterial co-infections previously reported in patients with *influenza* H1N1 and H3N2 [6–9], upon arrival of the COVID-19 pandemic, our hospital protocol recommended the initiation of antibiotic therapy for all hospitalised patients with COVID-19. Experience acquired within the first, few weeks led us to reconsider this approach, so as to administer empiric antibiotic therapy solely to patients admitted for COVID-19 and who present with a chest x-ray suggestive of bacterial infection, need for direct ICU admission or severe immunocompromised condition. Our results support the avoidance of antibiotic therapy in most patients hospitalised for COVID-19. The reason

for which bacterial co-infections are quite low in patients with COVID-19 is unknown; it is tempting to speculate that some immunological facts like macrophage hyperactivation play a role. Nonetheless, when bacterial co-infection is suspected, we recommend an antibiotic approach with optimal *S. aureus* coverage such as ceftaroline or ceftriaxone/cefazolin plus levofloxacin in areas with low MRSA prevalence.

Frequency of hospital-acquired superinfections remained low despite the fact that many patients were undergoing severe immunosuppressant treatments. Some factors may provide an explanation for that observation, including empiric antibiotic use, isolation measures or host macrophage activation. Further, the lack of additional microbiologic tests after SARS-CoV-2 was detected may have also contributed. Further studies will be needed to elucidate the role of each measure in decreasing superinfections. Superinfections have been mainly related with ICU admission, especially with the use of mechanical ventilation and catheters; expected epidemiology linked closely with predominant hospital flora. In our study, the rate of MDR infections was relatively low due to the possible impact of COVID-19 isolation measures precluding horizontal transmission among patients.

Aspergillosis complicating COVID-19 was clinically quite different and not as frequent as that observed in patients with *influenza* [12,13]. In patients with COVID-19, aspergillosis usually manifested as tracheobronchitis, especially in association with patients with prior lung disease, prolonged mechanical ventilation and high immunosuppressor dosage. In the opinion of this study's authors, this fact may also be in part related to the different immunologic dysfunction in influenza and COVID-19 infections [11,13,15]. Macrophages are the key host cell in fighting Aspergillus spp. due

237 to their involvement in *Aspergillus* spores recognition [16]. Patients admitted with
238 COVID-19 also had *Candida* spp. superinfections mainly related with parenteral
239 nutrition and urinary catheters.

240 Anecdotal cases of co-infections during SARS-CoV-2 and other virus infections have
241 been previously reported [16–19]. Our results support that respiratory virus
242 community-acquired co-infection is relatively uncommon in hospitalised patients with
243 COVID-19. However, viral co-infections could lead to severe diseases, and this study
244 was conducted in a mostly non-*influenza* season (incidence could vary in fall/winter).

245 Overall mortality in the cohort of patients hospitalised ≥48 hours was 9.8%. We found
246 that patients with other infections had worse outcomes, prolonged length of hospital
247 stay, higher rates of ICU admission and increased mortality. These finding are in
248 agreement with previous studies, which documented an association between co-
249 infection in respiratory virus pandemics and poor prognosis [6–8]. However, this is
250 unadjusted to baseline patients' characteristics and cannot be completely attributed to
251 co-infection and/or superinfections.

252 The strengths of this study comprise the large number of patients included, as well as
253 the clear, complete collection of clinical and microbiologic data. However, our study
254 does have some major limitations that should be acknowledged. First, this is a
255 retrospective study reporting clinically significant, microbiologically documented
256 infections. However, no systematic testing for co-infections was performed, and it is
257 possible that either some attending physicians did not order microbiologic tests for
258 their patients or some patients may have had co-infections or superinfections not
259 documented by performed microbiologic tests. A concern held among our team is

whether initial challenges arising during the management of patients with COVID-19 potentially decreased the number of requests for microbiologic tests to rule out other infections. Notwithstanding, infection rates reported in our study remained low, even in patients in whom urinary antigen testing or other types of test had been performed. Second, we described a cohort of patients currently discharged or dead. Some patients with severe COVID-19 infection that required ICU admission, mechanical ventilation and prolonged length of hospital stay remain hospitalised. It is conceptually easy to believe that superinfection is higher in this population. Third, respiratory RT-PCR techniques used were limited to the virus. PCR testing for the detection of atypical pathogens was not performed in our patients. Additionally, and as mentioned prior, we initially treated all hospitalised patients with antibiotics within the first, few weeks, for which the impact of such practice in preventing superinfections remains unknown. That stated, the first four limitations might underestimate the frequency of co-infections or superinfections in patients with COVID-19. Lastly, as this study was conducted at a single centre, there may have been influence when describing nosocomial infections. Frequency and microbiologic epidemiology may also vary significantly according to different geographical contexts.

In conclusion, bacterial, fungal and viral co-infections and superinfections in hospitalised patients with COVID-19 are low; however, when present, they may cause severe diseases with worse outcomes. *S. pneumoniae* and *S. aureus* are the most common pathogens to cause community-acquired pneumonia co-infections. In our area, *P. aeruginosa* and *E. coli* were frequent bacteria that caused hospital-acquired superinfections. Our findings are important when defining the role of empiric antimicrobial therapy or stewardship strategies in hospitalised patients with COVID-19.

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Declaration of conflicts of interest: CGV has received honoraria for talks on behalf of Gilead Science, MSD, Novartis, Pfizer, Jannsen and Lilly, as well as a grant from Gilead Science and MSD. PPA has received honoraria for talks on behalf of Gilead Science and

MSD. JM has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis and Angellini. AS has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis, and Angellini, as well as grant support from Pfizer. Other authors do not declare conflict of interest.

Authors' contributions: *Writing – Original Draft:* C.G-V., E.M-G., P.P-A., and A.S.; *Writing – Review & Editing:* all authors; *Conceptualization:* C.G-V.; *Investigation:* C.G-V., E.M-G., P.P-A., N.G-P., M.C., M.F-P., I.G., F.M., I.M.; *Methodology:* C.G-V., G.S., JA.M., A.S.; *Formal Analysis:* C.G-V., G.S., and E.M-G.; *Project Administration:* C.G-V., and A.S.; *Funding Acquisition:* C.G-V., F.G., A.S.

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Table 1. Main characteristic of patients hospitalized for COVID-19 more than 48 hours in our hospital.

Cohort characteristics	Patients without infection n=917	Patients with community-acquired co-infection n=31	P*	Patients with hospital-acquired superinfection n= 43	P**
Median age, years (IQR)	61 (48-74)	63 (54.5-74)	0.671	67 (55.75-74.25)	0.006
Male sex (%)	510 (55.6)	18 (58.1)	0.956	26 (60.5)	0.822
Comorbidities					
Hypertension (%)	167 (18.2)	7 (22.6)	0.537	7 (16.3)	0.748
Diabetes mellitus (%)	89 (9.7)	7 (22.6)	0.019	7 (16.3)	0.160
Chronic heart disease (%)	122 (13.3)	9 (29)	0.013	7 (16.3)	0.576
Chronic lung disease (%)	95 (10.4)	6 (19.4)	0.110	7 (16.3)	0.218
Chronic renal disease (%)	47 (5.1)	8 (25.8)	<0.001	6 (14)	0.013
Cancer (%)	77 (8.4)	1 (3.2)	0.259	8 (18.6)	0.021
Inflammatory markers at onset					
Median C-reactive protein (IQR)	7.06 (3.31-13.29)	6.76 (3.20-9.79)	0.714	11.78 (5.55-17.87)	0.012
Median ferritin (IQR)	544 (249.5-1100)	208 (154-431.5)	0.042	797 (296-1743)	0.575
Median lymphocyte count (IQR)	0.9 (0.6-1.2)	0.8 (0.6-1.1)	0.892	0.783 (0.5-1.1)	0.088

Median lactate dehydrogenase (IQR)	287 (233-372)	264 (221-377.5)	0.477	311.5 (247.5-471-8)	0.193
Treatment at onset					
Lopinavir-ritonavir (%)	732 (79.8)	27 (87.1)	0.227	35 (81.4)	0.802
Hydroxychloroquine (%)	799 (87.1)	29 (93.5)	0.225	40 (93)	0.186
Azythromicin (%)	751 (81.9)	26 (83.9)	0.779	36 (83.7)	0.761
Remdesivir (%)	39 (4.3)	0 (0)	0.226	2 (4.7)	0.559
Ceftriaxone (%)	528 (57.6)	24 (77.4)	0.028	32 (74.4)	0.029
Ceftaroline (%)	26 (2.8)	2 (6.5)	0.232	5 (11.6)	0.001
Immunomodulatory treatment					
Tocilizumab (%)	200 (21.8)	5 (16.1)	0.450	16 (37.2)	0.018
Methylprednisolone (%)	238 (26)	9 (29)	0.701	25 (58.1)	<0.001
Dexamethasone (%)	23 (2.5)	4 (12.9)	0.01	8 (18.6)	<0.001
Median length of hospital stay (IQR)	9 (5-15)	8 (4.5-11.5)	0.565	20 (11-27.75)	<0.001
Intensive Care Unit (ICU) admission (%)	109 (11.9)	8 (25.8)	0.02	29 (67.4)	<0.001
Median Length of ICU admission (IQR)	3 (1-10)	3 (0-9)	0.888	5 (0.5-20)	0.095
Death (%)	86 (9.4)	5 (16.1)	0.21	8 (18.6)	0.047

Two patients with community-acquired co-infection developed hospital-acquired superinfections.

*Comparison of patients without infection versus patients with community-acquired co-infection.

**Comparison of patients without infection versus patients with hospital-acquired superinfection.

Table 2. Number of microbiology tests ordered and positive results with clinical significance in patients with COVID-19.

Test	Number of patients with positive results/total patients	Number of patients with positive results/ tested patients	Number of tests with positive results/total tests
Blood cultures	16/989 (1.6%)	16/267 (5.9%)	37/680 (5.5%)
Urine cultures	19/989 (1.9%)	19/337 (5.6%)	19/717 (2.6%)
Respiratory samples (non-COVID)	25/989 (2.5%)	25/252 (9.9%)	23/845 (2.7%)
Pneumococcal urinary antigen	12/989 (1.2%)	12/230 (5.2%)	12/234 (5.1%)
***Influenza* A PCR**	4/989 (0.4%)	4/248 (1.6%)	5/252 (1.9%)
***Influenza* B PCR**	2/989 (0.2%)	2/250 (0.8%)	2/255 (0.8%)
Respiratory syncytial virus PCR	1/989 (0.1%)	1/251 (0.4%)	1/256 (3.9%)
Other respiratory virus PCR*	0/989	0/5	0/16

*5 patients underwent PCR testing for *Influenza C*, human *Metapneumovirus* and *Parainfluenza* 1, 2, 3 and 4. All were negative.

Table 3. Detailed epidemiology of microbiological documented bacterial infections in patients hospitalized with COVID-19.

Bacterial co-infection*	N=74 (%)
Infections at COVID-19 diagnosis	30/74 (40.5)
Community-acquired pneumonia co-infections	21/30 (70)
S. pneumoniae	12/21 (57.1)
S. aureus	6/21 (28.6)
H. influenzae	2/21 (9.5)
M. catarrhalis	1/21 (4.8)
Lower respiratory co-infection in patients with bronchiectasis	2/30 (6.6)
P. aeruginosa	2/2 (100)
Concurrent urinary tract infection	7/30 (23.3)
E. coli	1/7 (14.2)
K. pneumoniae	1/7 (14.2)
E. faecium	1/7 (14.2)
P. mirabilis	1/7 (14.2)
C. koseri	1/7 (14.2)
S. aureus	1/7 (14.2)
Hospital-acquired superinfections complicating patients admitted for COVID-19	44/74 (59.5)
Ventilator-associated pneumonia	11/44 (25)
S. aureus	4/11 (36.4)
P. aeruginosa	3/11 (27.3)
S. maltophilia	2/11 (18.2)
K. pneumoniae	1/11 (9)
S. marcescens	1/11 (9)
Hospital-acquired pneumonia	4/44 (9)
S. aureus	1/4 (25)
P. aeruginosa	1/4 (25)
S. maltophilia	1/4 (25)
K. pneumoniae	1/4 (25)

Bacteremia	16/44 (36.3)
Coagulase-negative staphylococci	7/16 (43.7)
P. aeruginosa	3/16 (18.7)
E. faecium	3/16 (18.7)
E. coli	2/16 (12.5)
S. anginosus	1/16 (6.2)
Urinary tract infection	12/44 (27.3)
E. coli	4/12 (33.5)
K. pneumoniae	3/12 (25)
E. faecalis	2/12 (16.7)
E. faecium	1/12 (8.3)
P. aeruginosa	1/12 (8.3)
S. marcescens	1/12 (8.3)
Polymicrobial intra-abdominal infection *(E. coli, E. faecium, E. faecalis)*	1/44 (2.3)

*Some patients had more than one bacterial infection.