INTRODUCTION

In the last years there has been a growing amount of evidence for “enteropathogenetic” infections caused by Candida spp., Clostridium difficile and carbapenemase-producing Klebsiella pneumoniae [1-5]. The common pathogenetic pathway is represented by an alteration of the intestinal flora, now mainly referred as the human microbiome which may now be analyzed by next generation sequencing (NGS) technique that perhaps will be further detailed by a series of project such as the Human Microbiome Project (HMP) and MetaHIT [6-9]. Recently we proposed the acronym “CCC” to suggest complex enteropathogenetic relationships amongst Candida, C. difficile and carbapenemases-producing Enterobacteriaceae [10]. The incidence of candidemia has increased over the past two decades, especially in Internal Medicine wards (IMW) where the prevalence is ranging from 24% to 57% and the numbers of cases are highest amongst the different wards, the mortality is in the range of 30-50% and, amongst cases presenting within the first 10 days after the hospital admission, as many as 51% were diagnosed in IMW [1]. So far, there are no sound diagnostic strategies, except for a recent proposal of preemptive and presumptive treatment in addition to prophylaxis, empiric and targeted treatment [11]. Most of candidemia and invasive candidiasis (IC) arise from the intestinal tract (endogenous pathogenesis) and few cases are primarily candidaeemic, for example from a central venous catheter (CVC): for example, the same Candida albicans was identified from the intestinal tract or skin and the bloodstream in a recent study, whereas the strains of Candida parapsilosis were different when the CVC was infected [12, 13].

Clostridium difficile is a spore-forming Gram-positive anaerobic bacillus that causes gastrointestinal infections in humans, ranging from asymptomatic colonization to severe diarrhoea, pseudomembranous colitis, toxic megacolon, colonic perforation, and death [14]. C. difficile is another important opportunistic pathogen once the microbiota has been changed. The human gut microbiota prevents pathogen invasion through direct inhibition, nutrient depletion or by stimulating host immune defences [15]. Without previous or con-
comitant antibiotic treatment, *C. difficile* is no capable of invasive disease. The microbiome changes may favor a chronic *C. difficile* infection (CDI) and the dissemination of disease, also modifying intestinal metabolites including biliary salts, and short chain fatty acids [16-18]. Carbapenemases-producing *K. pneumoniae* (c-Kp) is the new frontier of antibiotic-resistance: these bacteria are resistant to all beta-lactams and most other antibiotics except colistin and gentamicin; there are more questions than answers on the utility of carbapenems in combination treatment with colistin, tigecycline or both [19-21]. Clinical features of infections by c-Kp include the frequent finding of previous gastrointestinal colonization and some patients have fever as the only sign of infection, or may present with sepsis, severe sepsis or septic shock: the source may be pulmonary, abdominal, urinary or from the CVC [22]. One of the current medical need is to provide definitions of disease to avoid both overtreatment of colonized patients, which only need contact isolation measures, and undertreatment of colonized patients presenting with few signs of infection.

### EPIDEMIOLOGY

**Candidemia**

In a recent large study on the epidemiology of candidemia, there were 66% of cases (N=1175) hospital-acquired (≥3 days after the admission, HA); 29% (N=787) healthcare-associated community-onset (HCA-CO), which were defined within 3 days after the admission if resident in nursing home, had CVC ≥2 days, were hospitalised, had surgery or haemodialysis within the preceding 90 days or were transferred from an acute care hospital (also including neonates aged ≤30 days); and 4% (N=113) community-onset, diagnosed within 3 days with any of the above criteria [23]. The latter cases mostly had diabetes, cancer or previous surgery, had a mean age of 68 years vs. 58 years of HA and HCA-CO (p<0.001) and *Candida glabrata* was predominant (40%) followed by *C. albicans* (32%) and *C. parapsilosis* (13%).

![Figure 1 - Incidence of candidemia in Internal Medical Ward, years 2004-2012. Black line: Incidence of candidemia/1000 admission. Grey line: Incidence of candidemia/1000 days of hospital admission.](image)
In the intensive care unit (ICU), the incidence of candidemia ranges from five to 10 cases per 1000 admissions or 3-15 episodes per 10,000 patient days, corresponding to 5-10 times the incidence on general hospital wards [24]. When we studied patients with early-onset candidaemia (EOC) defined as disease occurring within 10 days by the hospital admission, as many as 51% (94 out of 183) of EOCs were admitted in IMWs and, interestingly, such patients (median time at risk compared to patients with late-onset disease, 6 vs. 27 days, p<0.001) had a higher chance of inappropriate treatment compared to late-onset disease [25].

Whereas in most papers candidemia occurs after 3-4 weeks after hospital admission, there are other reports of EOC, such as in ICU in India where candidemia occurs a mean of 8 days after admission, with an incidence of 6.51 cases /1,000 ICU admission, and from Australia and France [26-28].

In our 9-year study on 274 episodes of candidaemia in IMW (41% of the total hospital cases) the mean age was 68±17 years and the incidence was 1.8 episodes/1000 hospital admission or 0.16 episodes/1000 days and was variable in the different years, perhaps according to the policy of discharge and outpatient care (Figure 1) [1]. Diagnosis was made after a mean of 24±28 days and there were 68 patients with EOC (24.8%). The majority of patients had at least one or more comorbidities at hospital admission and the majority of patients had a urinary (77.7%) or central venous catheter (CVC) (71.2%).

*C. albicans* was the leading cause of infection (61%) followed by *C. parapsilosis* (20%) and *C. glabrata* (10%).

Clostridium difficile

*C. difficile* is the most frequently identified cause of nosocomial diarrhoea in hospitals and long-term care facilities and, according to the Centers for Disease Control (CDC) and Prevention, CDI is an “urgent threat”, urging actions to prevent the disease [14]. Antibiotic administration is a well-known risk factor for CDI and antibiotics at greatest risk should be managed by antimicrobial stewardship programs, especially in IMWs. The community also plays a significant role for CDI because of comorbidities, home-care, antibiotic treatment and comorbidities. The CDC reports that CDI is associated with 14000 deaths in US each year and more than $1 billion in excess medical costs [29].

Most of the CDI are health-care related, although there are emerging community cases, with rates ranging from 2.8 to 9.3 per 10,000 patient-days [14]. In one recent study in the Kaiser Permanente Southern California healthcare system, the rate of community-onset, health-care associated or hospital-acquired, health-care associated CDI was 11.1 versus 6.8 per 10,000 inpatient-days, respectively [30]. Recent data suggest the rate of community-acquired CDI at 20–30 per 100,000 population [31].

In a ribotyping study on 252 isolates in Turin during 2008-2010, there were 15 different ribotypes with a predominance of 018 (41%) and 3% of ribotype 027 [32]. Regarding the antibiotic susceptibility testing, there was a high level of resistance to fluoroquinolones, not only associated with ribotype 027. All strains were susceptible to vancomycin and metronidazole.

Carbapenemases-producing Klebsiella pneumoniae

The distribution of c-Kp is now a public health concern worldwide; in Europe, determinants now vary substantially by geography [33]. According to European Antimicrobial Resistance Surveillance Network (EARS-Net), the European population-weighted mean percentage for carbapenem resistance was 6.2% in 2012. Italy is in second place after Greece in terms of resistance (28.8%), much higher than other European countries. It is noteworthy that in Italy the c-Kp resistance grew rapidly in only three years (from 1% in 2009 to nearly 19% in 2012) [34].

A countrywide cross-sectional survey was carried out from 15 May to 30 June 2011 in Italy to investigate the diffusion of carbapenem-resistant Enterobacteriaceae (CRE) and to characterize the most prevalent resistance mechanisms and their dissemination patterns [35]. Twenty-five large clinical microbiology laboratories, distributed across the national territory, participated in the study. There were 270 (2.0%) consecutive non-replicated clinical isolates of CRE, highlighting an increase proportion of CRE among isolates from inpatients (3.5%). KPC-Kp was the most represented species (globally: 11.9%) and contributed to the majority of CRE (234 of 270, 86.7%) [36].

A regional surveillance program 2012 for c-Kp in Piedmont region, north-west of Italy, involving 28 regional Public Health Infection Control Units covering all the area (4,374,000 inhabitants) inves-
tigated the epidemiology in this region. During the year 2012, 8179 K. pneumoniae strains were reported, of which 17.5% were c-Kp. The incidence was 1.9/1,000 patients admitted to hospital; c-Kp was more frequently isolated in tertiary care referral hospitals and from urine samples (50%). Even if there was a decreasing trend at local level due to the implementation of infection control measures in 2012 when compared to 2011, as many as 31% of c-Kp strains were identified in IMWs, followed by ICUs (15%), surgical wards (13%) and emergency departments (14%) [20]. This report highlighted possible epidemiology changes, with more medical wards affected than ICUs when the CRE diffusion is no longer restricted to major hospitals but also challenges tertiary care hospitals and their infection control strategies.

**RISK FACTORS**

*Candidemia and invasive candidiasis*

Risk factors for IC and candidemia are well known and include colonization of body sites and major abdominal surgery, antibiotic treatment, diabetes, burns, ICU stay, invasive devices, organ failure, prolonged hospital stay, immunosuppression, neutropenia, disruption of mucosal barriers, non-abdominal surgery, major trauma, multiple transfusions, parenteral nutrition, haemodyalisis, CVCs, young and old age, vascular catheters [37]. However, IC is difficult to predict and early diagnosis remains a major challenge. Specific patient profiles have been studied in ICUs, surgical wards and oncohaematological or transplant units [24]. Unfortunately, non-candidaemic IC represents the majority of cases in the ICU, where early empirical antifungal treatment is currently suggested to reduce mortality. However, since microbiological evidence may be lacking in most cases, early empirical treatment currently relies on the positive predictive value of risk assessment strategies, such as colonization index, candida score, and predictive rules which have been recently reviewed [24]. As the Authors correctly underscore, these risk-based strategies are based on combinations of risk factors, such as Candida colonization, broad-spectrum antibiotic treatment and previous (abdominal) surgery but their negative predictive values are much higher than the positive predictive values, for which they were developed [24]. It is worth mentioning also the threat of antifungal resistance in ICU, recently reviewed [38]. The role of Candida colonization index was recently reviewed in its perhaps successful use to characterize colonization dynamics and to help understand the significance of candiduria [39]. We agree that the colonization index helps to understand the dynamics of colonization, which may be of great help in selected patients [24].

At large, the concepts and the above mentioned risk factors for disease may be similar in IMWs, where the risk factors for mortality have been recently studied [1]. The mortality was 39% (108/274) and was associated at multivariate analysis with sepsis, cirrhosis and neurologic diseases, whilst removal of CVC within 48h by the diagnosis and appropriate treatment were significantly associated with survival. In the 77 patients treated with empiric appropriate antifungal therapy the mortality was 29%, whilst it was 39% with appropriate definitive treatment. When no antifungal treatment was administered, the mortality was 49%. After excluding untreated patients, definitive echinocandin treatment was significantly associated with survival (OR 0.473; 95%CI 0.222-1.000).

*Clostridium difficile*

Risk factors for CDI may be divided into three general categories: host factors (immune status, co-morbidities), exposure to CD spores (hospitalizations, community sources, long-term care facilities) and factors that disrupt normal colonic microbiome (antibiotics, other medications, surgery) [40]. Factors that increase risk of exposure to C. difficile spores, such as increased duration of hospital stay may increase the risk of CDI. A length of stay ≥2 weeks has been shown to be a risk factor for CDI [41]. Despite this, in hospitals with well implemented infection control measures, very few cases of in-hospital C. difficile are consequent to such contact [42].

Although nearly all antibiotics have been associated with CDI, clindamycin, third-generation cephalosporins, penicillins and fluoroquinolones have traditionally been considered at greatest risk [43-49]. The use of associations of antibiotics and an antimicrobial treatment >10 days has also been associated with increased risk [50-51]. Antibiotics which have been less commonly associated with
Candidaemia, Clostridium difficile infection and carbapenemase-producing Enterobacteriaceae

CDI include macrolides, sulfonamides and tetracyclines.

In 2012 a systematic review of incident and recurrent CDI in protein pump inhibitors (PPI) users was published and 42 observational studies (30 case-control, 12 cohort) with 313,000 participants overall were included [52]. Despite the substantial statistical and clinical heterogeneity, the findings indicated a probable association between PPI use and incident and recurrent CDI. This risk was further increased by concomitant use of antibiotics and PPI. Other studies suggested that this association may be the result of confounding with the underlying severity of illness and duration of hospital stay [53]. Given that acid suppression drugs, especially PPIs, may be over-prescribed in surgical settings consideration should be given to stop or review the need for PPIs in patients at high risk of CDI. It is interesting that antimicrobial treatment was an important risk associated in the United States, whereas PPI exposure was a greater risk in Europe [54].

Recurrence of symptoms after initial therapy for C. difficile develops in 10-30% of cases and presents a clinical challenge: patients may have several episodes of recurrence that may occur over a period of years [55-60].

Carbapenemase-producing Klebsiella pneumoniae

Risk factors for colonization by c-KP were investigated in a retrospective, multicentric Italian matched (1:2) case-control study on c-Kp isolated from clinical samples of 657 patients, of which 426 representing true infections [61]. There appeared as independent predictors of isolation recent admission to an ICU, indwelling urinary catheter, CVC and/or surgical drain, ≥2 recent hospitalizations, haematological cancer and recent fluoroquinolone and/or carbapenem therapy.

Very few data are available for the risk factors for c-Kp bloodstream infection (BSI) among rectal carriers. In an Italian multicentric study the risk factors for c-Kp BSI amongst rectal carriers were studied [62]. Overall, 143 c-Kp BSIs were compared with 572 controls without a documented infection and at multivariate analysis ICU admission (OR, 1.65; 95%CI, 1.05-2.59; p=0.03), abdominal invasive procedure (OR, 1.87; 95%CI, 1.16-3.04; p=0.01), chemotherapy/radiation therapy (OR, 3.07; 95%CI, 1.78-5.29; p<0.0001), and number of additional colonization sites (OR, 3.37 per site; 95%CI, 2.56-4.43; p<0.0001) were found to be independent risk factors for c-Kp BSI amongst rectal carriers. This was the most important study to highlight that colonization at multiple sites with c-Kp was the strongest predictor of BSI development in our large cohort of c-Kp rectal carriers.

CLINICAL SYNDROMES

Candida infection

There are a number of issues that make the diagnosis of IC challenging: IC is difficult to prove without positive blood cultures, especially in

![Figure 2 - Candidaemia and invasive candidiasis as a continuum, illustrated by increasing mortality with increasing severity of disease. Diagnosis is based on sensitivity and specificity of blood cultures, biomarkers and clinical scores.](image-url)
critically ill patients; moreover, as many as 80% of critically ill patients may be colonized and few may develop invasive disease highlighting the unmet medical need, without biomarkers, of differentiating a continuum ranging from colonization to possible infection in patients with unstable diseases [14]. Challenges are even greater in patients in IMW, where no scores or prediction rules have been applied so far. The continuum of IC and candidaemia may be illustrated with a spectrum of clinical manifestations ranging from paucity of signs and symptoms where diagnosis is difficult and treatment should be easy, to sepsis, severe sepsis and septic shock where microbiological diagnosis may be easier and treatment is very likely to be inappropriate by timing (Figure 2). Moreover, in a recent NEJM study the Authors investigated the utility of the definition of sepsis and severe sepsis as based on the SIRS criteria, and concluded that the need for two or more SIRS criteria to define severe sepsis excluded one in eight otherwise similar patients with infection, organ failure, and substantial mortality, failing to define a transition point in the risk of death [22]. When we studied 365 patients with candidaemia with a hierarchical cluster analysis (Figure 3) we found that a significantly different set of variables was built starting with the presence or absence of SIRS criteria, followed by other clusters according to other statistically significant variables. Age, C. albicans aetiology, cirrhosis, kidney failure and other parameters should then be analyzed with different weight on mortality, if we exclude the importance of appropriate treatment. This method may be useful to illustrate candidemia by a different point of view. Furthermore, a critical agenda has been proposed for patients with intra-abdominal candidiasis, the guideline-forgotten candidiasis, focusing on risk factors, diagnosis and treatment strategies, also

Figure 3 - Hierarchical cluster analysis for risk factors for mortality in 365 patients with candidemia, 2004-2008, Molinette Hospital, Turin, Italy [11].
including prophylaxis [5, 63]. The pathogenesis of intra-abdominal candidiasis was reviewed for the specific risk factors and may be applied to IMW patients.

**Clostridium difficile**
The spectrum of symptomatic CDI ranges from mild diarrhoea to severe disease or fulminant colitis. As many as 30% of patients may develop recurrent CDI [14].

**Carbapenemases-producing K. pneumoniae**
Clinical syndromes caused by c-Kp range from asymptomatic gastrointestinal colonization to sepsis, severe sepsis and septic shock. Patients may also have pneumonia, abdominal infections, surgical infections, BSIs and CVC-BSI as well as infections of any device. In the immunocompromised patients there are reports of muscle abscesses and deep-seated infections. With such a wide range of clinical manifestations, emphasis should be given to standardized definitions which are still lacking. We propose to use a step-to-step diagnosis, where patients colonized and without any sign of infection should not be treated and only managed according to international guidelines of infection control, whereas colonized patients with any sign of infection, including fever as the only sign of disease, should be managed with intravenous antibiotic treatment, mainly combination treatment with or without a carbapenem which is a matter of debate (Figure 4) [19-64].

### FOCUSING ON CCC AS A UNIQUE ENTEROPATHOGENETIC MODEL OF OPPORTUNISTIC INFECTIONS

The gut microbiota regulates important physiological metabolic functions of the host and can be impaired during prolonged antibiotic treatments, becoming a significant reservoir of microorganisms with a nosocomial profile of antibiotic resistance. In *C. difficile* infections there is a clearly recognized causal role of a dysbiotic microbiota, suggesting that similar alterations may be favoring colonization by c-Kp or an excessive intestinal growth by *Candida* spp., thus favoring *Candida* BSIs. Indeed, there are reports of candidaemia following *C. difficile* severe infections, and c-Kp BSIs associated with candidaemia [2-65].

The identification of patients colonized by c-Kp in different settings deserves a dedicated intervention and a major compliance of health-care workers to simple standard hygiene procedures, such as hand washing [64]. There are guidelines on infection control issues for Gram-negative bacteria and for *C. difficile* [64, 66].

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![Figure 4 - Example of definitions of levels of interventions for patients colonized or infected by c-Kp.](image)
Candidaemia may follow severe CDI and CDI may be complicated by c-Kp BSI [2, 4]; there are early infections by c-Kp and early health-care associated BSIs by c-Kp [3-67]. For these reasons, we used “from KPC to CCC” to highlight the enteropathogenetic importance of Candida, C. difficile and carbapenemase-producing c-Kp [10]. Appropriate considerations and suggestions have been published in the critical care setting [68]. Here we propose to use the term “enteropathogenetic opportunistic syndromes” to highlight the importance of gastrointestinal alterations in promoting intestinal colonization, overgrowth and disease by Candida spp., C. difficile and carbapenemase-producing Enterobacteriaceae. It is a matter of infection control procedures and antimicrobial stewardship programs in IMWs. By an infection control point of view, we suggest to follow the European guidelines on prevention of colonization and infection by MDR Gram-negative bacteria: although they did not mention the intestinal tract in its current enteropathogenetic opportunistic view, the Authors highlighted the current level of evidence of infection control measures that should always be applied [64].

The antimicrobial stewardship approach should be used to understand that whenever there are IMW patients undergoing antibiotic treatment we should emphasize the concepts of de-escalation, improving diagnostic specificity rather than sensitivity, perhaps using serum biomarkers to avoid unnecessary, complex and redundant combination antibiotic treatment. It is a matter of personal choice but we can start smart with antimicrobial stewardship trying to reduce the opportunity for enteropathogenetic syndromes, especially reducing antibiotic use [69]. Accordingly, therapeutic levels of interventions, either contact precautions or treatment, should be decided for patients with c-Kp isolation (Figure 4).

There are a series of other considerations regarding the possible interaction amongst the CCC pathogens, such as the possible interactions amongst antibiotics use to treat CDI and Candida colonization [70]. Fidaxomicin treatment resulted in a lower percentage of Candida colonization compared to vancomycin (19% vs 29%, respectively). The result was also found in those patients colonized by Candida before fidaxomicin treatment, where the Candida colonization was reduced from 4.1 to 2.1 log_{10} CFU/g of stool and from 4.3 to 3.2 log_{10} CFU/g of stool with fidaxomicin or vancomycin, respectively. In another study it was hypothesized a possible protective effect of Candida overgrowth on the development of CDI [71]. In another case-control study there was a positive correlation between Candida colonization and CDI [72]. The severity of CDI, 027 ribotype and high-dose vancomycin (>1g/day) were significantly associated with the development of candidaemia in another study [73]. Furthermore, in a Greek ICU the intestinal colonization by c-Kp was associated with candidaemia and non-albicans species isolation [65].

In conclusion, before we perhaps will be forced to consider stool transplant beyond CDI, we should try to start with antimicrobial stewardship by increasing diagnostic specificity of infections, whereas if no clinical or laboratory signs of infections are found, no antibiotic treatment is administered or ongoing antibiotics are stopped. We should also reinforce infection control guidelines and contact precautions and appropriate screening should be optimized aiming at prevention of enteropathogenetic opportunistic infections, represented so far by Candida, C. difficile and carbapenemase-producing K. pneumoniae. Save the tube!

Acknowledgements

This work is dedicated to the memory of Gabriele Brondino.

Keywords: candidemia, C. difficile infection, carbapenemases, KPC-Kp, opportunistic infection, enteropathogenesis.
In this paper we analyze three “enteropathogenetic” opportunistic infections represented by Candida spp., C. difficile and carbapenemase-producing K. pneumoniae. The common pathogenetic pathway is based on an alteration of the intestinal flora, now mainly referred as the human microbiome, with secondary opportunism for infections caused by Candida, C. difficile and carbapenemase-producing Enterobacteriaceae (“CCC”). We highlight the epidemiology, risk factors, clinical syndromes associated with the pathogens and we propose some new issues related to the epidemiology and diagnosis of candidemia, also using hierarchical cluster analysis, definitions of levels of interventions in patients colonized or infected by carbapenemase-producing bacteria. The “enteropathogenetic” opportunistic syndromes are prevented with antimicrobial stewardship programs aiming at increasing diagnostic specificity of infectious syndromes to reduce the antimicrobial use and costs. Appropriate guidelines for infection control should also be implemented to reduce the nosocomial spread of “enteropathogenetic” microbes.

**SUMMARY**

**REFERENCES**


[13] Nucci M., Anaissie E. Revisiting the source of can-
surveillance in Atlanta and Baltimore, 2008-2011. Changes in incidence and antifungal drug resistance in
1629-1638, 2015.
372, 2011.
Bellomo R. Systemic inflammatory response syndrome
[22] Kaukonen K.M., Bailey M., Pilcher D., Cooper D.J.,
2013.
Euro. Surveill
moniae in Italy: results of the first countrywide survey, 15 May
in Italy: beyond the ICU.
Clin. Microbiol. In-
pneumoniae
in Italy: results of the first countrywide survey, 15 May
2011.
one-year survey of carbapenemase-producing Klebsiella
pneumoniae in Italy: beyond the ICU. Clin. Microbiol. In-
fect. 21, e11-3, 2015.
mortality in bloodstream infections caused by Kleb-
siella pneumoniae carbapenemase-producing K. pneu-
tion of Klebsiella pneumoniae infection. Infect. Control Hosp.
Epidemiol. 32, 201-206, 2011.
mortality in bloodstream infections caused by Kleb-
siella pneumoniae carbapenemase-producing K. pneu-
Society for Infectious Diseases guidelines for the diag-
nosis and treatment of Clostridium difficile infection.
infection and colonization. N. Engl. J. Med. 365, 1693-
1703, 2011.
[14] Evans C.T., Safdar N. Current Trends in the Epidemi-
ology and Outcomes of Clostridium difficile Infection.
W.E. Nosocomial acquisition of Clostridium difficile
tion of Clostridium difficile infection. Infect. Control Hosp.
Epidemiol. 32, 201-206, 2011.
[22] Kaukonen K.M., Bailey M., Pilcher D., Cooper D.J.,
2013.
Euro. Surveill
moniae in Italy: results of the first countrywide survey, 15 May
in Italy: beyond the ICU.
Clin. Microbiol. In-
pneumoniae
in Italy: results of the first countrywide survey, 15 May
2011.
one-year survey of carbapenemase-producing Klebsiella
pneumoniae in Italy: beyond the ICU. Clin. Microbiol. In-
fect. 21, e11-3, 2015.
mortality in bloodstream infections caused by Kleb-
siella pneumoniae carbapenemase-producing K. pneu-
tion of Clostridium difficile infection. Infect. Control Hosp.
Epidemiol. 32, 201-206, 2011.
mortality in bloodstream infections caused by Kleb-
siella pneumoniae carbapenemase-producing K. pneu-
Society for Infectious Diseases guidelines for the diag-
nosis and treatment of Clostridium difficile infection.
infection and colonization. N. Engl. J. Med. 365, 1693-
1703, 2011.
[14] Evans C.T., Safdar N. Current Trends in the Epidemi-
ology and Outcomes of Clostridium difficile Infection.
W.E. Nosocomial acquisition of Clostridium difficile
tion of Clostridium difficile infection. Infect. Control Hosp.
Epidemiol. 32, 201-206, 2011.
[22] Kaukonen K.M., Bailey M., Pilcher D., Cooper D.J.,
2013.
Euro. Surveill
moniae in Italy: results of the first countrywide survey, 15 May
in Italy: beyond the ICU.
Clin. Microbiol. In-
pneumoniae
in Italy: results of the first countrywide survey, 15 May
2011.
one-year survey of carbapenemase-producing Klebsiella
pneumoniae in Italy: beyond the ICU. Clin. Microbiol. In-
fect. 21, e11-3, 2015.
mortality in bloodstream infections caused by Kleb-
siella pneumoniae carbapenemase-producing K. pneu-
tion of Clostridium difficile infection. Infect. Control Hosp.
Epidemiol. 32, 201-206, 2011.
mortality in bloodstream infections caused by Kleb-
siella pneumoniae carbapenemase-producing K. pneu-
Society for Infectious Diseases guidelines for the diag-
nosis and treatment of Clostridium difficile infection.
infection and colonization. N. Engl. J. Med. 365, 1693-
1703, 2011.
[14] Evans C.T., Safdar N. Current Trends in the Epidemi-
ology and Outcomes of Clostridium difficile Infection.


