

# Correlations Between Colonization and Infection with Multidrug Resistant Bacteria in Immunocompromised Patients

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## ABSTRACT

Healthcare associated-infections, in particular for immunocompromised patients, such as patients with hematological/solid malignancies, patients with solid organ transplant or with liver cirrhosis, are fatal in most occasions. Because *Enterobacteriales* plays an important role in nosocomial infections, especially with the rising prevalence of carbapenem-resistant strains, we gathered recent findings from over the world, which are reviewed under the pressure of a major public health concern.

**Keywords:** MDR; Bacteria; Immunocompromised patients; Hematological Cancer; Solid Organ Transplant

**Abbreviations:** MDR: Multidrug Resistant; ESBL: Extended-Spectrum  $\beta$ -Lactamase; MRSA: Methicillin-Resistant *Staphylococcus aureus*; VRE: Vancomycin-Resistant Enterococci; SOT: Solid-Organ Transplant; CRE: Carbapenem-Resistant *Enterobacteriales*

## Introduction

Due to medical progress, the life expectancy of immunocompromised patients has increased. However, these patients have a high risk of infections with multidrug resistant (MDR) bacteria, which leads to an increased rate of morbidity and mortality. The increased incidence of antibiotic resistance in bacteria is a major problem in terms of treatment options, especially in immunocompromised patients such as HIV-positive patients, oncologic patients or those with a history of organ transplantation. This category of patients has an increased risk of infection with MDR bacteria due to prolonged immunosuppression, increased exposure to antibiotics,

and frequent contact with the healthcare system. Infections with MDR bacteria pose major problems in establishing appropriate treatment and increase the mortality rate of patients [1]. Oncologic patients have a state of immunosuppression caused by malnutrition, invasive procedures, surgery, chemotherapy and radiation, which makes them exposed to frequent complications such as bacterial infections with MDR microorganisms [2]. Currently, the most widely accepted definition of MDR bacteria include a lack of susceptibility in three or more antimicrobial categories active against the isolated microorganism [3]. The epidemiology of nosocomial infections among cancer patients has changed over the years, with

a predominance of Gram-negative bacteria in the 1960s and 1970s, then a shift to Gram-positive bacteria, and after 10 years, a return to Gram-negative bacteria. which nowadays are the dominant pathogens associated with bacterial infections among oncologic patients [4,5]. The predominant Gram-negative bacteria isolated from up to 80% of polymicrobial bacteremia, are extended-spectrum  $\beta$ -lactamase (ESBL) producing *Enterobacterales*, more frequently *Escherichia coli* and *Klebsiella* spp., and, also, carbapenem-resistant *Pseudomonas aeruginosa*. Other MDR *Enterobacterales*, *Stenotrophomonas maltophilia*, and *Acinetobacter baumannii* can also be isolated [6]. From Gram-positive bacteria, a particular challenge are the infections with methicillin-resistant *Staphylococcus aureus* (MRSA), which represent up to 50% of all staphylococcal infections, and vancomycin-resistant enterococci (VRE), which represent nearly 30% of infections in the United States [7]. Colonization with ESBL-producing *Enterobacterales* represent an important risk factor for systemic infections with these pathogens. Immunocompromised patients have a poor diversity of the intestinal microbiome, which is mostly dominated by Gram-negative bacteria, and translocation of these pathogens into the bloodstream is a risk factor for life-threatening systemic infections. Also, prior skin and mucosal colonization with opportunistic bacteria like Gram-negative ones frequently precedes infection [8]. Several studies on bone marrow transplant patients have shown that colonization with VRE, was associated with VRE bacteremia [9]. Moreover, prior exposure to antibiotics increased the risk of bacteremia with Gram-negative bacteria among oncologic patients.

Patients who had undergone a solid-organ transplant (SOT) have a long-term immunosuppressive state and are more exposed to infections with MDR bacteria. These infections represent the leading cause of morbidity and mortality among SOT recipients and threaten the chance of graft survival. Among liver and kidney transplant patients, the most frequent infections are with ESBL-producing *Enterobacterales* and carbapenem-resistant *Enterobacterales* [10]. Studies on patients undergoing hematopoietic stem cell transplantation shown that colonization with MDR bacteria was an extremely important factor for the outcome of these patients and was stated that stem cell transplantation might be contraindicated or postponed in case of infection with ESBL-producing *Enterobacterales* or carbapenem-resistant *Enterobacterales* (CRE). In case of colonization with CRE, stem cell transplantation is not contraindicated, but a thorough evaluation of the risk-benefit ratio must be performed [11,12].

### Epidemiological Situation for Immunocompromised Patients

A study conducted from 2002 to 2011 in Tunisia revealed a higher prevalence of MDR Gram-negative bacilli (165 MDR strains of a total of 676 strains) among hematopoietic stem cell transplant

patients, with a percentage of 34.5% *Klebsiella pneumoniae* and 11.46% *Escherichia coli* ESBL-producing strains, 32.8% *Pseudomonas aeruginosa* strains resistant to imipenem and/or ceftazidime and also 20.75% methicillin-resistant *Staphylococcus aureus* strains [13]. Regarding the patients with SOT, multiple studies highlighted the colonization/infections with ESBL-producing *Enterobacterales* and with CRE [14]. One of the studies revealed that for patients with kidney transplant the most common infections are those with ESBL-producing *Enterobacterales* from the urinary tract, especially post-transplant, ranging from 3% to 11% [15,16]. For patients with liver transplant, Aguado, et al [17]. showed that 5.1% of the colonized patients got an infection with ESBL-producing *Enterobacterales*, in contrast with 2.4% of the non-colonized patients [17]. In Italy, by 2015, the prevalence of CRE strains in patients with solid organ transplant was 26.5%, and *Klebsiella* spp. was the one who registered the highest percentage (49.1%) [18]. In a multicentric prospective observational study of 144 hematological patients, bloodstream infections appeared in 25.7% patients, after the rectal colonization with: ESBL-producing *Enterobacterales* (41%), CRE (59%) and vancomycin-resistant enterococci (6%) [19].

A particular study from Serbia examined 65 patients with Liver cirrhosis and hospital-acquired urinary tract infections, patients who are at high risk of developing various infections. *Enterococcus* spp. (52.3%), *Klebsiella* spp. (15.4%), *Escherichia coli* (9.2%), *Proteus mirabilis* (7.7%) and methicillin-resistant *Staphylococcus aureus* (MRSA) (3.1%) were the main species that were isolated and 53.8% from the Gram-negative bacilli were MDR and only one strain of *Klebsiella* spp. was Extensively Drug Resistant (XDR) [20]. Another study, from Iran, highlighted a concerning rise in the prevalence of metallo- $\beta$ -lactamase (MBL) producing strains in oncologic patients (66.8% *Proteus* spp., 28.6% *Klebsiella pneumoniae*, 27.7% *Escherichia coli* MBL-positive). The MBL-positive strains (79% from the urinary tract) were isolated from patients with skin cancer (21%), blood cancer (21%) and prostate cancer (15.8%). All the Gram-negative bacilli (100) that were isolated were multidrug resistant and 60% of them were carbapenem-resistant [21]. Between 2015 and 2016, in Egypt, 102 strains of Gram-negative bacteria from bloodstream infections were isolated from febrile neutropenic cancer patients and 70 were multidrug resistant; *Escherichia coli* was the most frequent pathogen with a percentage of 38.6%, followed by *Klebsiella pneumoniae* with 34.3%, *Acinetobacter baumannii* with 12.8%, *Enterobacter cloacae* with 5.7% and *Pseudomonas aeruginosa* with 2.8% [22]. Haddad, et al [23]. Conducted a study on 165 patients with hematological cancer and bloodstream infections during 2007-2017.

They showed that 65% of the infections were caused by Gram-negative bacilli, with a predominance of *Escherichia coli*

(45.6%), followed by *Pseudomonas aeruginosa* with 7.5% and *Acinetobacter baumannii* with 4%. 61% of the strains were multidrug resistant, and 79.6% of *Escherichia coli* strains were ESBL-producing strains [23].

## Conclusion

According with data collected worldwide from immunocompromised patients, *Escherichia coli* and *Klebsiella pneumoniae* were the most frequently isolated MDR strains, especially from bloodstream infections and urinary tract infections. The alarming increase of MDR strains isolated from immunocompromised patients highlight the importance of appropriate empirical antimicrobial therapy, as well as a systematic screening regarding the carriage of MDR bacteria, in order to reduce colonization with these pathogens, and therefore reducing the risk of potential bacterial infections that can be fatal to these patients.

## Conflict of Interest

We declare that there is no conflict of interest regarding the publication of this article.

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