21 Gram-Negative Bacterial Infections After Hematopoietic Stem Cell or Solid Organ Transplantation

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21.1 Introduction

21.1.1 Epidemiology of Gram-Negative Rods Infections

Gram-negative rods (GNR) cause significant morbidity and mortality in hematopoietic stem cell (HSCT) and solid organ transplant recipients (SOTR) [1–7]. These patients are prone to infection with GNR as a result of neutropenia, mucositis, the use of invasive devices and due to operation in SOTR [8]. Invasive GNR infections usually arise from abdomen (including infections of the hepatobiliary system in liver transplant recipients) [9], the urinary tract (especially occurring in renal transplant recipients) and lungs (occurring in all transplant groups, but notably in lung transplant recipients). In SOTR, complications (for example, portal vein thrombosis in liver transplant recipients) and prolonged mechanical ventilation represent significant risks. Risk factors for invasive GNR infection in neutropenic patients include age >45 years, recent administration of beta-lactams, chills, urinary symptoms, absence of gut decontamination with both colimycin and aminoglycosides [10] and previous colonization [11]. In the early years of transplantation, GNR were the leading cause of serious bacterial infection in both bone marrow and SOT recipients [12]. Later, gram-positive pathogens have become more frequent [13, 14]. Reemergence of GNR is reported in recent years [15–18]. A recent review of studies published during 2005–2011, on bacterial infections in patients with hematological malignancies or post HSCT, reported gram-positive to GNR ratios in adults 60 %:40 %, with a huge variation between centers, from 85 %:15 % to 26 %:74 % [17]. The corresponding numbers in children were: 58 %:42 %, ranging from 86 %:14 % to 32 %:68 % in individual studies. The main GN pathogens causing bacteremia in HSCT recipients (expressed as median prevalence, with range) were *Enterobacteriaceae* (24 %, 6–54 %), followed by *Pseudomonas aeruginosa* (10 %, 0–30 %) [17]. An ECIL-4 survey performed in 2011 on surveillance of bacteremia in hematology and HSCT patients summarized recent data from 39 European centers. As compared to published data, it showed a slight reduction of the gram-positive to GNR ratio (55 %:45 % vs. 60 %:40 %) and an increased rates of Enterobacteriaceae (30 % vs. 24 %), and decreased rate of *Pseudomonas aeruginosa* (5 % vs. 10 %) [17].

GNR are important cause of infections in SOTR [19]. 15.4 % of 956 SOTR developed GNR infection in one study [20]. The unadjusted overall incidence of gram-negative BSI was 15.8/1000 person-years following SOT [21]. In a recent multicenter Italian study, recipients of either heart or lung graft were at the highest risk to develop GNR bacteremia [20]. In another study, however, the rate of GNR infections was highest in simultaneous kidney–pancreas (40/1000 person/years) and lowest in liver and heart (12/1000 person years) recipients [21]. Others reported that 50–60 % of all BSI in liver Tx patients were due to GNR [7, 22]. The majority of infections with the GNR in transplant recipients occur in the early posttransplant period, especially in the first month post transplantation [9, 15, 16, 20, 21, 23].

21.1.2 Clinical Manifestations and Outcome

GNR infections may present with diverse clinical pictures: bacteremia with or without concomitant local site infections. One study reported pulmonary infections in 28.4 %, urinary tract infections in 14.8 %, and skin or soft tissue infections in 9.7 % [24]. Other studies have reported that septic shock was specifically associated with infection with GNR [25] or with drug-resistant GNR infections [26].

Infection with GNR is associated with worse prognosis. Mortality rate in HSCT patients experiencing GNR BSI was 59 % in one study [27]. In other studies, 7-and 30-day mortality after BSI onset was 17–22 % and 24–31 % [23, 28]. In one study, among aerobic gram-negative pathogens, *Pseudomonas aeruginosa* had the highest associated mortality rate (40 %) followed by the *Enterobacter, Citrobacter, Serratia* group with 25 % mortality and *E. coli* or *Klebsiella* with 3 % mortality within a 7-day period [15]. The overall unadjusted 28-day all-cause mortality of GNR BSI was

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4.9 % in SOTR and was lower in kidney than in liver recipients (1.6 % vs. 13.2 %, $p < 0.001$) [21]. However, another study reported lower mortality 2/70 (3 %) patients [29].

21.1.3 Antimicrobial Resistance

21.1.3.1 Definitions

The isolate is considered multidrug-resistant (MDR) if it is non-susceptible to at least one agent in ≥3 therapeutically relevant antimicrobial categories; extensively drug-resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories); and pandrug-resistant (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories [30].

21.1.3.2 Mechanisms of Resistance

The major mechanism of resistance to cephalosporins is beta-lactamase production. The most important beta-lactamases are the plasmid-mediated extended-spectrum beta-lactamases (ESBLs), including CTX-M, TEM and SHV and inducible group 1 AmpC cephalosporinases, which are resistant to beta-lactamase inhibitors [31–39]. Class B beta-lactamases (metallo beta lactamases, MBLs) hydrolyze all penicillins, cephalosporins, and carbapenems, with the exception of monobactam aztreonam. The most common types of MBL are IMP and VIM groups [40].

The usual mechanism of resistance to quinolones is mutation of the genes that encode the target enzymes (DNA gyrase and topoisomerase IV) for quinolones.

21.1.3.3 Epidemiology of Resistance

There is a growing problem of increasing resistance to antibiotics all over the world, including in oncological and transplant patients. There is a significant site-to-site variation in the epidemiology of resistance. Prevalence of resistance is influenced by the local policy of antibiotic use for prophylaxis and treatment, infectious control measures, as well as prevalence of resistance in the whole hospital and country.

Recent literature review of studies which report on the epidemiology of BSI in HSCT patients reported that 41 % (range 18–74 %) of GNR bacteria are resistant to fluoroquinolones, 28 % (6–41 %) to aminoglycosides, 43 % (17–45 %) to ceftazidime and 20 % (11–72 %) to carbapenems [17].

According to the ECIL-4 questionnaire assessing the recent situation in HSCT centers in Europe, median rates of ESBL-producers among *Enterobacteriaceae* was 15–24 %, aminoglycoside-resistant GNRs 5–14 % and carbapenem-resistant *Pseudomonas aeruginosa* 5–14 %. Resistance rates were significantly higher in South-East vs. North-West European HSCT centers [17]. The resistant pathogens causing most clinical problems were reported to be ESBL-producing *Enterobacteriaceae* in 28 (76 %) of centers, whilst the next-most frequent concerns were fluoroquinolone-resistant GNRs, ($n = 17$, 46 %), carbapenem-resistant *Pseudomonas aeruginosa* ($n = 15$, 41 %) and much less multidrug-resistant (MDR) *Acinetobacter baumannii* ($n = 5$, 14 %).

Several studies report on increase in MDR GNR rods in HSCT patients, including ESBL-producing *Enterobacteriaceae*, AmpC cephalosporinase hyperproducing *Enterobacteriaceae*, MDR *P. aeruginosa, Stenotrophomonas maltophilia*, and *Acinetobacter baumannii* [18, 41–43].

21.1.3.4 Risk Factors for Resistance

The most important risk factor for infection with resistant pathogens is prior colonization or infection by resistant organisms such as ESBL- and carbapenemase-producing Enterobacteriaceae, colistin-resistant *Klebsiella pneumoniae*; resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* [44–56].

Another important risk factor for infection with resistant GN in transplant patients is previous exposure to broad spectrum antibiotics for treatment or prophylaxis [18, 40, 42, 57–66]. Especially important in this context is the potential role of fluoroquinolone prophylaxis in HSCT recipients [16, 60, 67–72].

Treatment with third-generation cephalosporins was associated with infection due to MDR GNR pathogens [73].

Other risk factors for resistant GNR pathogens in HSCT patients include serious illness (e.g., end-stage disease, sepsis, pneumonia), nosocomial infection, prolonged hospital stay and/or repeated hospitalizations, intensive care unit (ICU) stay, urinary catheters, and older age [18, 42, 45, 46, 48–55, 60, 61, 70–75].

In SOTR, risk factors for infection with resistant GNR include nosocomial acquisition, longer hospital stay, admission to hospital for more than 48 h before transplantation, previous transplantation, prior ICU admission, septic shock, age greater than 50 years, HCV infection, devices, increased severity of the underlying disease, renal failure with or without dialysis [20, 26, 62, 64, 66, 76–78].

In renal Tx recipients, risk factors for resistant GNR infections were double kidney–pancreas transplantation, requirement for posttransplant hemodialysis, surgical reoperation, posttransplant urinary obstruction, and requirement for nephrostomy [64, 77]. Lung transplant recipients had a higher risk for isolation of carbapenem-resistant bacteria in one study [20].

21.1.3.5 Impact of Resistance

Infections caused by resistant GNR, including ESBL-producing Enterobacteriaceae, MDR NFGNR, carbapenem-resistant GN, are associated with increased mortality in both HSCT and SOT patients [7, 22, 41, 42, 61, 64, 79–85].

Many of these studies show that failure to cover GNR pathogens, particularly ESBL producers, MDR *P. aeruginosa*, and CRE in empiric treatments significantly and independently impairs outcomes patients, increasing mortality and prolonging hospitalization [43, 60, 61, 71, 72, 80, 86–89]. Infection with multiresistant bacteria was associated with graft loss in kidney transplant recipients [64].

21.1.4 Treatment

Serious infections due to the GNR rods in transplant recipients should be managed with a beta-lactam or quinolone antibiotic, active in vitro against the infecting organism.

Several studies demonstrate that onco-hematological and transplant patients infected with resistant and MDR GNR are significantly more likely to receive an inadequate initial empiric antibiotic therapy than those with a susceptible strain [18, 26, 42, 60, 61, 71]. These studies also show that the time to appropriate therapy is much longer where the pathogen is resistant.

21.2 Enterobacteriaceae

21.2.1 Epidemiology

The members of the *Enterobacteriaceae* are GNR bacilli which are usually resident in the gastrointestinal tract. Examples of such organisms include *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae, Proteus mirabilis*, and *Citrobacter freundii*. The majority of infections are caused by *E. coli*, followed by *Klebsiella* spp. and *Enterobacter*/*Citrobacter*/*Serratia* spp. [15, 21].

The majority of BSI in SOTR are due to *Enterobacteriaceae* [7, 20–22], they mainly occur during the first month after SOT [7, 22]. The risk is highest in transplant recipients whose peritoneal cavity has been breached (liver, intestinal, and pancreatic transplant recipients). Spillage of enteric organisms into the peritoneal cavity in such patients may lead to intra-abdominal abscess formation and manipulation of the biliary tree may lead to cholangitis.

Pneumonia occurring early after lung transplantation and urinary tract infections in renal transplant recipients may be more likely to be due to the *Enterobacteriaceae* [90, 91].

21.2.2 Clinical Manifestations and Outcome

Infections with the *Enterobacteriaceae* in transplant recipients have a multitude of clinical presentations. The sites of infection have been diverse and have included the urinary tract, lower respiratory tract, intra-abdominal, bloodstream, and wounds.

All transplant recipients, by virtue of prolonged hospitalization, may develop skin and upper respiratory tract colonization with gastrointestinal tract flora. Therefore, central venous line related infections and ventilator-associated pneumonia may occur due to the *Enterobacteriaceae*. Liver transplant recipients are prone to development of intra-abdominal infections with the *Enterobacteriaceae*. These may be mixed infections with anaerobes and enterococci. Examples of such infections include peritonitis, intra-abdominal abscess, cholangitis, and infected bilomas. Renal transplant recipients may develop complicated urinary tract infections or develop secondary infections within urinary leaks. The most common infections with the *Enterobacteriaceae* in lung and heart transplant recipients are pulmonary infections, which occur in all other SOT [92].

Death in neutropenic or other heavily immunosuppressed patients may occur within hours of onset of signs of infection, in the absence of appropriate supportive and antibiotic treatment. *Enterobacter* bacteremia was associated with 63 % mortality rate in one SOTR study [12].

21.2.3 Antimicrobial Resistance

21.2.3.1 Mechanisms of Resistance

The increasing resistance to carbapenems in *Enterobacteriaceae*, especially but not limited to *K. pneumoniae*, is a major concern. Resistance to carbapenems may be mediated by several mechanisms, including production of carbapenemases, efflux pump, decreased membrane permeability, and combination of these mechanisms [93]. Combination of plasmid-encoded AmpC or ESBL expression together with decreased cell membrane permeability may be also responsible for resistance to carbapenems [94]. The main mechanism of carbapenem resistance in *Enterobacteriaceae* in most parts in the world is hydrolysis by the serine class A β-lactamase *Klebsiella pneumoniae* carbapenemase (KPC). This mechanism also conferred resistance to all cephalosporins, aztreonam, and beta-lactamase inhibitors such as clavulanic acid and tazobactam. The gene encoding this enzyme *bla*KPC is located on plasmids and can be transferred between different species [94, 95]. Specifically, KPC-producing *Klebsiella pneumoniae* clone, sequence type ST258, has emerged and disseminated worldwide, being responsible for several outbreaks, including in HSCT patients [96–99].

Since 2009, a novel plasmid-encoded enzyme, New Delhi MBL (NDM), has spread through India, Pakistan, and the UK, and was reported also in transplant patients [100, 101]. These strains typically also have 16S rRNA methylases, conferring complete aminoglycoside resistance [102].

Carbapenem- resistant *Enterobacteriacea* (CRE) are frequently resistant to other antibiotics, including those considered as a “last resource,” as colistin, tigecycline, fosfomycin, and aminoglycosides.

21.2.3.2 Epidemiology of Resistance

Two to 44 % of *Enterobacteriaceae* in HSCT patients are ESBL producers [15, 16, 41, 73, 79, 81, 83, 103]. There is significant increase in carbapenem-resistant GNRs, especially *Klebsiella pneumoniae* (CRKp), in some HSCT centers [104].

In one study, CRKp infection was independently associated with recent stem-cell transplantation or organ, and it found to be associated with numerous health care-related risk factors and with high mortality [105].

In a recent retrospective Italian survey, more than a half of 52 centers reported on CRKp infections, and the incidence is growing, especially in allogeneic HSCT patients [43]. The incidence of CRKp infections was 0.4 % (from 0.1 % in 2010 to 0.7 % in 2013) in auto-SCT and 2 % (from 0.4 % in 2010 to 2.9 % in 2013) in allo-SCT populations [43].

ESBL producing organisms frequently colonize the gastrointestinal tract of SOTR.

The rate of ESBL-producers among Enterobacteriaceae in SOTR is 8–77 % [21, 22, 29, 77, 106–111]. 42.3 % of 80 MDR GNR strains isolated from 350 SOT recipients were ESBL-positive (mainly *Enterobacteriaceae*) [39].

There is increasing quinolones resistance of GNR bacteria in SOT [21, 112]. One study reported on increasing resistance among *Escherichia coli* isolates to fluoroquinolone antibiotics from 0 to 44 % ($p=0.002$) throughout the study period (1996–2007) [21].

Several studies reported on infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) in SOT patients. In one cohort study, organ transplant recipients appeared to be at increased risk for CRKp bacteremia [113]. Incidence of CRE infections was 1.3–12.9 % in liver, 9.4–26.3 % in kidney, 0.4–6.6 % lung, 7.5–16.7 % in heart transplant patients [100, 114]. In one recent multicenter Italian study, 26 % of all GNR bacteria and half of all *Klebsiella pneumoniae* in SOT patients were carbapenem-resistant [20]. SOTR were involved in hospital outbreak with CRE [115]. The median time since SOT to infection was 12–90 days, late infection 218 days after lung transplant was reported however [116]. The site of infection was bacteremia in 17–100 %. The other sites were pneumonia 25–50 % in liver, lung, and heart SOT; UTI in 60–100 % in renal transplants, intraabdominal (mainly in liver transplants) and soft tissue infections.

Colonization with CRKp endangers patients with subsequent infection. Generally, patient colonized with CRKp has 7.8–16 % chance to develop CRKp BSI [117, 118]. In transplant patients this risk is higher. The rates of BSI among rectal CRKp carriers was 39 % in hematological and allo-HSCT patients, 26 % in auto-HSCT, 18.8 % in SOTR, 18.5 % in ICU and 16 % in general ward patients [43, 117–119]. Patients with documented CRKp infection before allogeneic HSCT with had high chance of relapse—45.4 %; 90 % of them died despite early targeted therapy [43].

In liver transplant patients, CRKp infection rates among patients non-colonized, colonized at the time of transplantation, and colonized after transplantation were 2, 18.2, and 46.7 % in one study ($p<0.001$) [120]. In another study in liver Tx, 8/9 patients known to be colonized with KPC-2 CRKp developed infection, and five (56 %) were confirmed to have BSI with KPC-2-KP [84].

Certain factors predispose CRKp colonized patients to develop infection, such as number of colonization sites, admission to the ICU, abdominal invasive procedure, chemotherapy/radiation therapy, diabetes mellitus, solid tumor, tracheostomy, urinary catheterization, having a central venous catheter, receipt of antibiotics, renal replacement therapy; mechanical ventilation >48 h; hepatitis C virus (HCV) recurrence [117, 118, 120]. Some of these factors are routinely present in transplant patients, which can explain higher risks of invasive infection following colonization. In patients with health care-associated bacteremia, prior use of carbapenems may be only second to cephalosporins as the most significant antibiotic exposure associated with the involvement of ESBL-producing organisms [48].

21.2.3.3 Impact of Resistance

Mortality rate in infections caused by ESBL-producing bacteria was 38–52 % as compared to 5.5–29 % in infections caused by non-ESBL producing bacteria in HSCT recipients [41, 61, 79–81].

Mortality in infections caused by CRE was significantly higher as compared to non-CRE bacteria (33–72 % vs. 9–22 %) in several studies, including in transplant patients [43, 82, 104, 105, 121–123]. The infection-related mortality rates were 16 and 64.4 % in autologous and allogeneic HSCT recipients, respectively. Almost all patients died because of CRKp infection in one recent study [43]. The high rate of mortality in allo-HSCT patients was comparable or higher than that reported in previous series of intensive care unit (32–41 %), some solid organ transplant (40 %) and hematologic malignancies (65 %) patients [43, 100, 124]. The infection-related mortality rate was 48 % in patient who received CRKp- targeted 1st line therapy as compared with 73 % in those who received a not CRKp-targeted first-line antibiotic therapy ($p=0.002$) [43].

CRE bacteremia in SOTR caused septic shock in 18 % of patients, and was recurrent and persistent in 29 % each, in one study [116]. Summary of several studies in SOTR infected with CRE reported on 37 % mortality [100], in one study it reached 78 % [84]. SOTR with at least one positive culture for carbapenem-resistant GNR had a 10.23-fold higher mortality rate than those who did not [20]. Bacteremic or non-bacteremic infections due to CRKp resulted in a five-fold increased risk of death after liver transplantation [125]. Retrospective cohort study comparing SOTR with a first episode of UTI due to CRKp, ESBL-producing *Klebsiella*

pneumoniae, or susceptible *Klebsiella pneumoniae* demonstrated that CRKP is associated with long length of stay, and microbiological failure [78]. Six of 13 (46 %) kidney transplant recipients with CRKp infection, and none of the patients with carbapenem-sensitive *Klebsiella pneumoniae* infection, died within 6.5 months of infection onset [126]. Resistance to colistin has been independently associated with worse outcomes in patients infected with CRKp [127].

21.2.4 Treatment

An important caveat is that ESBL-producing organisms may appear susceptible in vitro to third generation cephalosporins (ceftazidime, cefotaxime or ceftriaxone) or cefepime, yet be functionally resistant to these agents [128]. 8–20 % of patients receiving broad-spectrum cephalosporins for *Enterobacter* infection had resistant isolates under treatment due to induction of AmpC [129–132].

ESBL producers in vitro are inhibited by beta-lactamase inhibitors (sulbactam, clavulanate, tazobactam). However, MIC to these agents rises with increasing inoculum [133]. Quinolones are usually inappropriate for treatment, as resistance to quinolone is frequent in ESBL producing bacteria: 20–90 % ESBL producers were resistant to quinolones, as compared to 2–42 % of non-ESBL-producers [61, 79, 134]. Carbapenems should be regarded as the drugs of choice for serious infections with β-lactamases-producing organisms [35, 37, 38, 121, 135].

Treatment of carbapenem-resistant GNR is discussed below. Resistance to agents active against carbapenem-resistant GNR has been reported. For example, among KPC-Kp isolates in HSCT patients, 80.8 % were susceptible to colistin, 69.2 % to tigecycline, and 65.4 % to gentamicin in one study [104].

Appropriate treatment for resistant bacteria is frequently delayed. Inadequate empirical therapy was most common in SOTR infected with ESBL bacteria [56]. CRKp-targeted therapy was provided with more than 2 days delay in one study in patients with hematological malignancies [124].

21.3 Non-fermentative Gram-Negative Rods (NFGNR)

21.3.1 Epidemiology

The NFGNR include *Pseudomonas aeruginosa, Acinetobacter* spp., *Burkholderia cepacia, Stenotrophomonas maltophilia*, and some other more rare bacteria. Non-fermentative refers to their inability to ferment glucose (instead, most species degrade glucose oxidatively). Non-fermentatives are less frequent causes of BSI than *Enterobacteriaceae* in transplant patients [7, 12, 15, 17, 20–22]. However, these are more frequent causes of pneumonia [20].

Pseudomonas aeruginosa is the most frequent of the NFGNR, causing about 5–15 % of bacteremias [7, 17, 20, 21]. *Acinetobacter* spp, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia* are considerably less frequent—responsible for about 2 % (0–12 %) of bacteremia in HSCT [18, 27, 136–145] and 2–10 % of GNR bacteremia in SOTR [7, 20].

Pseudomonas aeruginosa is responsible for 8–25 % of cases of pneumonia occurring in SOTR [92, 146]. Lung transplant recipients are at greatest risk [90, 147, 148].

Between 2 and 13 % of patients with cystic fibrosis (CF) are colonized with *Burkholderia cepacia* [149–151]. Increasing age and advanced lung disease are risk factors for *Burkholderia cepacia* colonization implying that candidates for lung transplantation may also be at the highest risk of *Burkholderia cepacia*.

21.3.2 Clinical Manifestations and Outcome

In one study on NFGNR bacteremia in cancer patients (including HSCT), the risk of complications was high (47 %), including 35 % with septic syndrome, 19 % pneumonia, 3.5 % enterocolitis, and 3.5 % soft-tissue infections [139]. There are few clinical characteristics which distinguish transplant recipients with infection with NFGNR from patients with infection with the *Enterobacteriaceae*.

Pseudomonas aeruginosa bacteremia may be associated with ecthyma gangrenosum. The skin lesions of ecthyma ganrenosum may be multiple, with rapid evolution through stages of macules, nodules, vesicles, and ulcerative eschars. The lesions contain little, if any, pus. In children the lesions tend to occur on the perineum and buttocks, but they may appear anywhere. Although ecthyma gangrenosum is regarded by some as pathognomonic for *Pseudomonas aeruginosa* bacteremia, similar lesions have been reported with other etiologies of bacteremia, such as *Stenotrophomonas maltophilia* [152].

In SOT patients, *Pseudomonas* can cause pneumonia, UTI (mainly in renal Tx) and bacteremia [64, 106]. *Pseudomonas aeruginosa* may be associated with cholangitis in liver transplant recipients. De novo colonization of the lung allograft by *Pseudomonas* is associated with the subsequent development of bronchiolitis obliterans [153].

Mortality is especially high in *Pseudomonas aeruginosa* bacteremia in both HSCT and SOTR: 39–67 % [12, 15, 16, 23, 28, 62, 154]; the majority of patients died within 7 days from the onset of infection. Mortality is especially high if caused by multidrug resistant (MDR) bacteria [83, 155]. Onset of *Pseudomonas aeruginosa* blood stream infections in ICU is an independent predictor of mortality after HSCT and SOT patients [62].

Acinetobacter spp, *Stenotrophomonas maltophilia*, and other NFGNR were responsible for catheter related bacteremia, severe sepsis, severe hemorrhagic pneumonia and soft

tissue infection in HSCT patients [18, 27, 136–145] and 2–10 % of GNR bacteremia in SOTR [7, 20, 156]. The most frequent clinical manifestation of *Stenotrophomonas maltophilia* is pneumonia and the second most frequent is CVC-related bacteremia [144, 156–158]. It must be recognized that not every isolate from the respiratory system is a true cause of pneumonia, but may represent colonization of respiratory tract.

Stenotrophomonas maltophilia emerges particularly in patients with prior broad-spectrum antimicrobial therapy.

Acinetobacter spp. can cause suppurative infections in virtually every organ system; mainly they cause nosocomial infections [9]. Lung transplant recipients infected with *Acinetobacter* were less likely to clear infection as compared to non-transplant patients, and more likely to die because of *Acinetobacter* infection [85]. Infections with *Acinetobacter* can be severe, a third of them were associated with septic shock and 47.1 % deaths in liver Tx recipients [9].

Burkholderia cepacia infection in lung transplant recipients may produce a rapidly progressive pneumonia, sometimes accompanied by septicemia. Occasional patients have lung abscess or empyema [159]. Both lung transplant recipients and lung transplant candidates may have simple colonization with *Burkholderia cepacia* however. Some lung transplant candidates have a gradual but progressive decline in their clinical condition after they become colonized with *Burkholderia cepacia*. These patients may have repeated hospital admissions with fever, declining respiratory function and weight loss. In contrast, some lung transplant candidates have a rapidly progressive syndrome known as the "cepacia syndrome" [160]. These patients present with high fever and respiratory failure. Laboratory testing reveals leukocytosis and a markedly elevated erythrocyte sedimentation rate (ESR). Person to person transmission of *Burkholderia cepacia* has been reported, most likely through direct contact with respiratory secretions [161]. Transplant patients with CF and chronic granulomatous disease are vulnerable to *Burkholderia cepacia* pneumonia, and bacteremia with this pathogen may also occur.

Specific comment should be made regarding colonization and lung infection due to *Burkholderia cepacia*. Some, but not all, studies of *Burkholderia cepacia* pneumonia in lung transplant recipients have shown elevated mortality compared to patients who were never colonized with this organism. There is a report on mortality of close to 50 % in *Burkholderia cepacia* colonized CF patients undergoing lung transplantation [159]. Others found that 1-year survival of *Burkholderia cepacia* colonized patients was 67 % compared to 92 % for patients not colonized with this organism [162]. Lung SOTR with CF who were infected with *Burkholderia cepacia* had poorer outcomes and represented the majority of those who had a septic death [163]. In contrast, a number of small studies have not shown significant difference in survival of *Burkholderia cepacia* colonized versus non-colonized patients [164, 165]. It appears that a subset of *Burkholderia cepacia*, genomovar III, is linked to inferior outcome [166, 167]. Patients colonized with *B. cenocepacia* before lung transplant were six times more likely to die within one year of transplant than those infected with other *Burkholderia cepacia* complex (Bcc) species ($p = 0.04$) and eight times than noninfected patients ($p < 0.00005$) [168]. 9/12 patients with *B. cenocepacia* infection died following lung transplantation, as compared to significantly better outcomes of recipients infected with other Bcc species, comparable to other recipients with CF [169]. Therefore, colonization with *B. cenocepacia* is considered as a contraindication for lung transplantation in some centers [169].

Following lung transplantation, infection with Bcc species other than *B. cenocepacia* does not significantly impact 5-year survival whereas infection with *B. cenocepacia* pre-transplant is associated with decreased survival [168].

21.3.3 Antimicrobial Resistance

21.3.3.1 Mechanisms of Resistance

Pseudomonas aeruginosa displays a diverse array of antibiotic resistance mechanisms [170]. Resistance to beta-lactam antibiotics is usually, but not exclusively, mediated by beta-lactamases. A frightening arrival has been the IMP and VIM type beta-lactamases which can hydrolyze carbapenems, and all other beta-lactams with the exception of aztreonam [171]. However the coexistence of other beta-lactamases usually results in resistance to aztreonam. Metallo beta-lactamase production was the main mechanism of resistance in NFGNR found in one study [39].

Imipenem resistance can be mediated by loss of OprD, a porin or outer membrane protein. Loss of OprD results in resistance to imipenem and reduced susceptibility (but usually not frank resistance) to meropenem. OprD may be co-regulated with an efflux pump called MexEF-OprN [170, 172]. Use of imipenem can select for loss of OprD, but not for upregulation of the efflux pump. In contrast, use of quinolones can select for upregulation of the efflux pump and also reduced OprD (resulting in resistance to both quinolones and imipenem). Frank resistance to meropenem usually requires both loss of OprD and upregulation of an efflux pump known as MexAB-OprM [172].

The efflux pumps are an important mechanism of multidrug resistance, since they may confer resistance to quinolones, antipseudomonal penicillins, cephalosporins, and sometimes also aminoglycosides. Quinolone resistance may also be mediated by mutations to the chromosomally mediated topoisomerases II and IV. Aminoglycoside resistance may be mediated by outer membrane impermeability or by aminoglycoside modifying enzymes.

Stenotrophomonas maltophilia is intrinsically resistant to carbapenems because of the production of carbapenem hydrolyzing beta-lactamases. *S. maltophilia* usually harbors

two types of beta-lactamases: L1, a metallo-beta-lactamase that hydrolyzes all beta-lactams except aztreonam and is not inhibited by clavulanic acid and L2, an inducible class A beta-lactamase that hydrolyzes aztreonam but is inhibited by clavulanic acid. Strains harboring these beta-lactamases hydrolyze almost all beta-lactams and beta-lactam–beta-lactamase inhibitor combinations. The majority of strains are susceptible to ticarcillin–clavulanate, but not to ampicillin–sulbactam or piperacillin–tazobactam. *Stenotrophomonas maltophilia* is frequently resistant to all aminoglycosides, probably due to impermeability of the outer membrane.

A variety of beta-lactamases have been reportedly produced by *Burkholderia cepacia* [173–179]. Resistance may also be mediated by membrane impermeability.

Acinetobacter spp. may be capable of virtually complete antibiotic resistance. Some authors have used the abbreviations CRAB (carbapenem-resistant *Acinetobacter baumannii*) or PDRAB (pandrug-resistant *Acinetobacter baumannii*) [180]. As is the case with *Pseudomonas aeruginosa*, resistance of *Acinetobacter* spp. may be mediated by a combination of beta-lactamases and outer membrane protein deficiencies. A clinically useful observation has been the in-vitro efficacy of ampicillin–sulbactam in the face of resistance to almost all other drug classes. Sulbactam is able to bind to penicillin binding protein 2 (PBP-2) and therefore can impart direct antimicrobial activity against *Acinetobacter* spp [181].

21.3.3.2 Epidemiology of Resistance

Transplant recipients (HSCT and SOT) are at greater risk of MDR *Pseudomonas aeruginosa* BSI, with an appreciable mortality. In a large study, resistance to all antibiotic classes was significantly greater in *Pseudomonas* BSI isolates from transplant compared with non-transplant patients ($p<0.001$). Of isolates from transplant recipients ($n=207$), 43 % were MDR, compared with 18 % of isolates from non-transplant patients ($n=391$) ($p<0.001$) [62].

In HSCT patients *Pseudomonas aeruginosa* is frequently resistant to several antibiotic classes. 18–72 % are resistant to fluoroquinolones, 11–50 % to aminoglycosides, 15–50 % to third-generation cephalosporins, 10–28 % to piperacillin tazobactam and 8–60 % to carbapenems [15, 16, 23, 24, 72, 182]; 25–71 % are MDR [16, 62, 72, 73, 143]. Outbreaks of multidrug resistant GNR rods (*Stenotrophomonas, Pseudomonas*) were reported in HSCT units [183–185].

In SOT patients NFGNR are frequently resistant to antibiotics; 31–74 % of them are MDR in some reports [26, 29, 62, 76, 83, 186, 187]; others report on XDR *Pseudomonas* and *Acinetobacter* [76, 83]. 37 % of 49 cases of *Acinetobacter baumannii* infection in kidney and liver transplant recipients were caused by carbapenem-resistant isolates in one study [89], while in another study in liver transplant patients, 75 % were carbapenem-resistant [9]. Infection with CRAB manifested mainly as pneumonia (83 %) in one study in SOTR, half of these patients subsequently developed CRAB BSI; 5/6 patients died [188]. CRAB caused 42.9 % of all *Acinetobacter* infections in abdominal SOTR as compared to 13.7 % among non-transplant ($p<0.01$) [188]. XDR *Acinetobacter baumannii* in infections were significantly more common among cardiothoracic than abdominal transplant recipients ($p=0.0004$). Ninety-eight percent (40/41) of patients had respiratory tract infections, most commonly ventilator-associated pneumonia (VAP); 88 % [36/41]) [189].

CF patients undergoing lung transplantation are frequently infected with MDR and PDR NFGNR, such as *Pseudomonas, Burkholderia*, and others. In some centers, 44–55 % of patients harbored PDR NFGNR, mostly *Pseudomonas* [106, 190, 191]. *Burkholderia cepacia* is frequently MDR [192, 193].

Contact with other patients colonized with resistant *Pseudomonas aeruginosa* may be risk factor for acquisition of resistant strain [194].

21.3.3.3 Impact of Resistance

Mortality in MDR *Pseudomonas* infections was 36 % vs. 12.5 % in non-MDR infections in HSCT patients [182].

MDR and XDR *Acinetobacter* infections is associated with high mortality rate of 49–95 % in HSCT and SOTR [136, 188, 189, 195]. Polymyxin-resistant *Acinetobacter* colonization or infection after liver transplantation was independently associated with mortality [196].

Some studies reported on decreased survival in CF patients infected with PDR bacteria [190], others however reported that their survival is similar to patients without PDR colonization [163, 191]. Inappropriate therapy was associated with increased mortality in SOTR patients infected with *Acinetobacter* spp. and MDR GNR [39, 89].

21.3.4 Treatment

21.3.4.1 Pseudomonas aeruginosa

There has been long-standing debate over the value of combination therapy in the treatment of serious *Pseudomonas aeruginosa* infections. Combination therapy had been considered the mainstay of therapy for many years, but recently proponents of monotherapy have emerged. Much of the support for combination therapy emanated from the prospective observational study of 200 consecutive patients with *Pseudomonas aeruginosa* bacteremia, showing that combination therapy was found to be significantly better than monotherapy in improving outcome. Mortality was significantly higher in patients given monotherapy (47 %) than in patients given combination therapy (27 %) [197]. It should be noted that the most common combination used was piperacillin or ticarcillin combined with tobramycin or gentamicin. The monotherapy group was dominated by patients

given an aminoglycoside alone. Few patients received cephalosporins, aztreonam, carbapenems, or quinolones [197]. In the contrary, there are two studies, including *Pseudomonas aeruginosa*, on GNR bacteremia, that did not find statistically significant differences in mortality between those receiving beta-lactam monotherapy versus beta-lactam-aminoglycoside combination therapy [198, 199]. No difference in mortality between monotherapy with beta-lactam and combination of beta-lactam with aminoglycoside or fluoroquinolone was demonstrated in the recent review of randomized and non-randomized studies [200].

To definitively show that combination therapy is superior to monotherapy would require a randomized controlled trial of several hundred patients. It is not likely that such a study will be ever performed. The demonstration of in-vitro synergy between antipseudomonal beta-lactam antibiotics and aminoglycosides, and the development of resistance with monotherapy, prompts us to continue to recommend combination antibiotic therapy for serious *Pseudomonas* infections. It is not clear whether the combination of two antibiotics needs to be continued for the entire treatment course or whether combination therapy in the first 3–5 days of treatment is sufficient. A combination of antipseudomonal beta-lactam plus aminoglycoside is the gold standard of therapy. Minimization of the aminoglycoside component of this regimen to 3–5 days should minimize risk of toxicity [201]. Combinations of beta-lactams and quinolones are sometimes used but the clinical data to support such combinations is sparse. We do not recommend combinations of two beta-lactams. Double beta-lactam therapy has proved inferior to the beta-lactam-aminoglycoside combination in animal models [202]. One study in humans showed emergence of resistance in 40 % (two of five) of cases in one series of *Pseudomonas aeruginosa* infection treated with double beta-lactams [203].

High doses of quinolones for therapy of serious *Pseudomonas* infections are recommended. For ciprofloxacin, an intravenous dose of 400 mg every 8 h is recommended instead of standard 400 mg every 12 h. Likewise we recommend levofloxacin at 750 mg per day, rather than 500 mg per day, for serious pseudomonal infections. For beta-lactams, the rate of bactericidal activity of beta-lactams does not increase substantially once concentrations exceed four times the MIC. Beta-lactams do not exhibit a postantibiotic effect against *Pseudomonas aeruginosa* with the notable exception of the carbapenems. Thus, high drug concentrations do not kill *Pseudomonas aeruginosa* any faster than low concentrations, and bacterial regrowth will begin very soon after serum and tissue levels fall below the MIC. The duration of time that serum levels exceed the MIC is the pharmacokinetic parameter that best correlates with in vivo efficacy of the beta-lactams. Continuous infusion of antipseudomonal beta-lactams is therefore theoretically attractive. At this time, this approach remains to be validated in large clinical studies. Aminoglycosides, even when in combination therapy, should be dosed once daily. Aminoglycosides exhibit concentration-dependent bactericidal activity, and also produce prolonged postantibiotic effects. This supports the practice of once daily aminoglycoside dosing.

21.3.4.2 Other NFGNR

There are no randomized controlled trials which can guide therapy of *Stenotrophomonas maltophilia*. Trimethoprim–sulfamethoxazole should be considered the primary therapeutic agent. Resistance may arise and the sulfonamide component is poorly tolerated by some patients [204–206]. However, it must be recognized that *Stenotrophomonas maltophilia* may be a colonizer of the airways, in which case not treatment is needed. Alternative agents against *Stenotrophomonas maltophilia* proposed by some authors include the beta-lactams, ticarcillin–clavulanate, and ceftazidime; fluoroquinolones, with moxifloxacin reportedly active in-vitro against some ciprofloxacin-resistant isolates from hematological patients [207]; minocycline and chloramphenicol. Combination therapy with either ticarcillin–clavulanate or with a third-generation cephalosporin (mainly ceftazidime) should be considered in a neutropenic or severely ill patients [204, 208, 209]. Published cases series on treatment regimens other than trimethoprim–sulfamethoxazole are small with variable success and drugs used often in combination [50, 204–206].

Burkholderia cepacia can be extremely resistant, but ceftazidime, carbapenems (imipenem and meropenem), ciprofloxacin, piperacillin, chloramphenicol, and trimethoprim–sulfamethoxazole have the greatest likelihood of in vitro activity. It is important to note that combination therapy is highly desirable because of the probability of emergence of more resistant isolates during therapy. *Burkholderia cepacia* is resistant to commonly used inhaled antibiotics (tobramycin and colistin) [106].

Carbapenems (for example, imipenem or meropenem) have traditionally been regarded as extremely potent agents in the treatment of severe infections due to *Acinetobacter* spp. This has been borne out in studies of *Acinetobacter* bacteremia [210]. Carbapenem-resistant *Acinetobacter baumannii* may remain susceptible to sulbactam [2, 168, 211] a beta-lactamase inhibitor that also has clinically relevant intrinsic antimicrobial activity against the organism. In patients with strains resistant to virtually all currently available antibiotics, colistin may be the only viable option [212]. In-vitro studies show potential advantages of combinations of rifampin with colistin [213]. A new antibiotic, tigecycline, shows usefulness against multiresistant *Acinetobacter* organisms [65, 214]. *A. baumannii* can develop resistance to tigecycline by mutation, with the trait sometimes selected in therapy [215–217]; moreover some regionally prevalent MDR strains are non-susceptible to tigecycline [218].

21.4 Treatment Options for Carbapenem-Resistant GNR

Treatment of carbapenem-resistant GNR is challenging. In some cases, the only treatment options include old antibiotics (polymyxins and fosfomycin), tigecycline, and aminoglycosides [50, 135, 219–221]. All these options have efficacy, resistance, and/or toxicity issues.

Summary on current treatment options for carbapenem-resistant GNR is presented in Table 21-1.

21.4.1 Polymyxins

The polymyxins were originally isolated from *Bacillus* spp—polymyxin B from *B. polymyxa* in 1947 and colistin (also known as polymyxin E) from *B. colistinus* in 1950. The polymyxins act primarily on the bacterial cell wall, leading to rapid permeability changes in the cytoplasmic membrane. Entry into the cell is not necessary. The polymyxins may also have antiendotoxin activity. Carbapenem-resistant GN can remain sensitive to colistin. Increasing number of reports on successful systemic polymyxins use, including in transplant patients [222–224]. Other usages of colistin reported were: as aerosols, in adjunction to systemic therapy in patients with pneumonia [225], intraventricular use for CNS infections [226] and endotoxin removal using polymyxin-B-based hemoperfusion [227]. Inhaled colistin in lung transplant patients may delay colonization with *Pseudomonas aeruginosa* [228]. The use of colistin raises several issues of concern:

1. Efficacy. Treatment with colistin was associated with increased mortality as compared with other appropriate regimens in several studies; some of them included onco-hematological patients [229, 230]. Others, however, reported on considerable effectiveness, depending on the daily dosage and infection site [222, 223, 231].
2. Toxicity, mainly nephrological and neurological. Nephrotoxicity, which was reported in up to 50 % of patients receiving colistin–polymyxin B in older studies,

Table 21-1. Main characteristics of the new or revisited antibacterial drugs for treatment of infections due to MDR GNR bacteria

	Colistin/polymyxin B [115, 220, 221, 232, 235, 236, 305]	Tigecycline [216, 220, 244, 306]	Fosfomycin [204, 231, 307, 308]
Class	Polymyxin	Tetracyclines	Phosphonic acid derivative
Mechanism of action, hydro/lipophilic	Disrupts bacterial membranes, hydrophilic	Protein synthesis inhibition, lipophilic	Inhibits peptidoglycan synthesis, Hydrophilic
Bactericidal/-static; concentration/time dependent activity	Bactericidal, concentration dependent	Bacteriostatic, time dependent	Bactericidal, variable concentration-dependent or time-dependent
Spectrum	Enterobacteriaceae, *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, not *Proteus, Serratia, Providencia* spp	Enterobacteriaceae, *A. baumannii, S. maltophilia,* not *P. aeruginosa, Proteus, Morganella*, and *Providencia* spp	Enterobacteriaceae (esp. *E. coli*), some *P. aeruginosa,* not *A. baumannii*
Half life	5.9 ± 2.6 h (Following administration of two million international units of colistin methanesulphonate)	37 ± 12 h	5.7 ± 2.8 h
Route of elimination	Renal	Biliary/fecal and renal	Renal and fecal
Dose and route	Wide dose range used (3–9 × 10^6 IU/day) Loading dose nine million IU and maintenance dose 4.5 million IU every 12 h preferred, IV	100 mg loading dose followed by 50 mg twice daily, IV	Range 2 g three times daily up to 4 g four times daily, IV
Main side effects	Nephrotoxicity, neurotoxicity	Nausea, vomiting and headache	Gastrointestinal (rare)
Warnings	Increased mortality as compared to other appropriate regimens in some retrospective studies Low colistin concentration after the first few doses in the routine dose regimen	Low blood levels Increased risk of death compared to other antibiotics used to treat severe infections	No clinical experience in this patient population Readily selects resistance
European Medicines Agency (EMA) labeled indications	Serious infections caused by GNR bacteria, including those of the lower respiratory tract and urinary tract where sensitivity testing suggests that they are caused by susceptible bacteria	Complicated skin and soft tissue infections, complicated intra-abdominal infections	No EMA license; individual country licenses include infections of lung, urinary tract, and bone, with associated bacteremia

Adapted from Averbuch D, Cordonnier C, Livermore DM, Mikulska M, Orasch C, Viscoli C et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). *Haematologica* 2013; 98(12): 1836–47.

is much less frequent in newer studies, including HSCT patients, with rates ranging from 10 to 30 % [221–224, 232].

3. Appropriate dose. The recommended dose in adults is nine million IU daily in two or three divided doses as a slow intravenous infusion; in critically ill patients a loading dose of nine million IU should be given. Doses should be reduced according to creatinine clearance in patients with renal impairment. In children, the suggested dose is 75,000 to 150,000 IU/kg daily, in three divided doses [233]. Loading dose and high daily dosages of colistin may help to overcome the problem of low blood levels that may have been responsible for the suboptimal efficacy of polymyxins, as well as to the selection of resistant strain variants [219, 234–237].
4. Emergence of colistin-resistant GN after previous exposure to colistin was reported [196, 234]. Susceptibility decreased during therapy with colistin in 40 % of SOTR infected with XDR *Acinetobacter baumannii* [195].

21.4.2 Tigecycline

Tigecycline has a broad spectrum of in vitro activity against MDR GNR bacteria, excluding *Pseudomonas aeruginosa, Proteus* spp., *Providencia* spp., *and Morganella* spp. [205, 238–240]. Standard dosage tigecycline, in combination with an anti-pseudomonal drug (ß-lactams, quinolones, aminoglycosides) achieved clinical response in 56 % of HSCT recipients [241]. Patients with pneumonia had lower response and higher mortality rates than those with bacteremia (51 % vs. 79 %, 44 % vs. 16 % respectively, both $p < 0.05$) [241]. In another study, standard dosage tigecycline used alone or combined with other antibiotics, showed clinical response (defined as partial or complete improvement of signs/symptoms of infection) in 16/23 (70 %) of bacteremia cases, 18/29 (67 %) of pneumonia and in 7/12 (58 %) where it was used for empirical treatment of febrile neutropenia [242],. The microbiologic response rate 70 % was achieved during treatment of CRKp infections after liver transplantation in the intensive care unit (ICU) with tigecycline, but 30 % died due to CRKp [243].

Higher-dosage tigecycline regimens potentially may be advantageous in severe infections. A recent randomized study in patients with hospital-acquired pneumonia showed that clinical cure with tigecycline 100 mg twice daily after a loading dose of 200 mg (17/20, 85.0 %) was numerically higher than with tigecycline 75 mg twice daily after a loading dose of 150 mg (16/23, 69.6 %) and imipenem–cilastatin (18/24, 75.0 %) [154]. However, evidence of increased mortality, compared to other antibiotic therapies, especially in VAP [244] leads to caution in its use. Moreover, a serious drawback, at least for monotherapy in bacteremia, is the low serum level obtained [216]. Superinfections with pathogens inherently resistant to tigecycline (*Pseudomonas aeruginosa*, *Proteus* spp., *Providencia* spp., and *Morganella* spp.) are another concern [215, 236, 243]. Breakthrough CRE bacteremia during tigecycline therapy was reported due to susceptible strains [113]. Increased MIC during treatment with tigecycline was reported in kidney Tx patient [245].

21.4.3 Fosfomycin

Fosfomycin is another old, but increasingly revisited, antibiotic with broad-spectrum in vitro activity against GNR bacteria, excluding *Acinetobacter* spp. Several studies estimate 80–90 % of Enterobacteriaceae with extended-spectrum beta-lactamases (ESBLs) and carbapenemases to be susceptible to fosfomycin [204, 219], but other studies report that only 50 % of *Klebsiella* spp. and fewer than 30 % of MDR *Pseudomonas aeruginosa* to be susceptible [135, 221]. Due to the possibility of resistance developing during therapy, fosfomycin should be used in combination with other agents, selected according to the susceptibility results [204, 246]. Data on the efficacy of intravenous fosfomycin are limited to case reports and small case series [204] and there is no published experience of treating invasive infections in oncohematological and HSCT patients. A retrospective study in HSCT patients showed, that in a multivariate analysis, exposure to fosfomycin (route of administration not specified) was associated with a significantly decreased incidence of veno-occlusive liver disease [247]. Fourteen cases of UTI in kidney Tx recipients were treated with fosfomycin, mostly due to *E.coli*, 50 % resistant to carbapenems. The overall clearance rate of UTI at 3 months was 31 %; recurrence occurred in 54 % and persistence occurred in 21 % of cases, no adverse drug reactions were reported [248]. In another report, 30 % microbiological cure was achieved when MDR GNR UTI was treated with fosfomycin in 15 SOTR; in 3 of them resistance to fosfomycin developed during treatment, and another one had superinfection due to fosfomycin-resistant bacteria [249].

21.4.4 Combination Therapy in Infections Due to Resistant GNR

21.4.4.1 In-Vitro Data

Some in vitro data suggest synergy in combining two agents (polymyxin B and either rifampin or doxycycline; fosfomycin with meropenem or colistin) against carbapenemase-producing *Klebsiella pneumoniae*, even when the pathogen is resistant to one of these agents [250, 251]. An ertapenem–doripenem combination may be of potential usefulness against KPC-producing *Klebsiella pneumoniae* based on a study in an immunocompetent murine thigh infection model based on the notion that the high affinity of KPC for ertapenem would “trap” the enzyme thus enhancing the activity of doripenem [252].

A recent meta-analysis of studies examining in vitro interactions of antibiotic combinations consisting of any carbapenem with colistin or polymyxin B against GNR reported that combination therapy showed synergy rates of 77 % for *Acinetobacter baumannii*, 44 % for *Klebsiella pneumoniae*, and 50 % for *Pseudomonas aeruginosa*, with low antagonism rates for all. Doripenem showed high synergy rates for all three bacteria. The use of combination therapy led to less resistance development in vitro [253].

Various combinations of rifampin, beta-lactams, aminoglycosides, quinolones, colistin–polymyxin B, fosfomycin, or other agents are synergistic in vitro, or in animal models, against MDR *Pseudomonas* or *Acinetobacter* spp. [135, 211, 254–258].

21.4.4.2 Clinical Data

In the era of increasing resistance, combination therapy is increasingly used for treatment of carbapenem-resistant and MDR GNR [221].

Several meta-analyses of randomized controlled studies, some of them done before the present era of increasing resistance, concluded that there was similar all-cause mortality in febrile neutropenic patients treated with a beta-lactam vs. the same beta-lactam plus an aminoglycoside as empirical or definitive therapy [148, 259, 260]. However, owing to the small numbers of cases of infection due to resistant bacteria, a benefit of combination therapy could not be ruled out for those patients who were critically ill or were infected with *Pseudomonas aeruginosa* or some other resistant pathogen [148, 259, 260].

In a recently published prospective multicenter study which compared empirical therapy with piperacillin–tazobactam with or without tigecycline in high-risk neutropenic patients with hematologic malignancies, the combination therapy proved to be more effective, including in patients with bacteremia and clinically documented infections [261].

A retrospective study reviewed patients with hematological malignancies or post-HSCT, who were infected by ESBL- or AmpC-producing Enterobacteriaceae or resistant *Pseudomonas*, most of whom were empirically treated with combination of a beta-lactam and an aminoglycoside. Mortality was lower among those patients whose pathogen was sensitive in vitro to either the beta-lactam or the aminoglycoside, compared with those whose pathogen was resistant to both (OR, 1.8; 95 % CI, 1.3 to 2.5) [87].

Carbapenem-containing combinations were associated with significantly reduced mortality compared to non-carbapenem-containing regimens in a retrospective analysis of 138 patients who received treatment for infections due to carbapenemase producing *Klebsiella pneumoniae* when the carbapenem MIC for the infecting organism was ≤4 mg/L [122]. Patients infected with CRKp who received combination therapy, especially with a combination of tigecycline, colistin, and meropenem, had lower mortality as compared to monotherapy treated group [262]. Combination antibiotic therapy improves the likelihood that at least one component agent is active in patients with severe sepsis or septic shock associated with GNR bacteremia [263].

The combination of a carbapenem and colistin was successfully used in SOT patients infected with CRKp and XDR *Acinetobacter baumannii* [116, 189, 195]. This combination was associated with improved survival in XDR *Acinetobacter baumannii* infections and decreased chance of development resistance to colistin as compared to other combinations [189]. In a recently published case-control study in critical patients in ICU infected with carbapenem resistant GNR, mainly *Pseudomonas aeruginosa*, combination therapy had been used significantly more often in survivors compared with non-survivors (32.1 % vs. 7.8 %, $p<0.01$) [264].

Rifampin was considered for addition to other active antibiotics in the treatment of uncontrolled infection due to MDR bacteria [211, 240, 250, 265–267]. However, a randomized, open-label clinical trial, which enrolled 210 patients with life-threatening infections due *Acinetobacter baumannii* that were susceptible only to colistin showed that 30-day mortality was not reduced by addition of rifampicin [268]. Similarly, another randomized controlled study comparing colistin to combination of colistin and rifampin for VAP caused by *Acinetobacter* did not show significant differences in mortality [269]. Other problems with rifampin include its toxic potential and drug interactions, a main concern especially in transplant patients who receive a lot of other drugs concomitantly (such as cyclosporine, mycophenolate mofetil, antifungals, antivirals) [268].

Although several studies reported on the improved outcome in patients who received combination therapy, mainly including colistin, a summary of the studies (12 retrospective cohort studies or case series, two prospective observational studies and two randomized controlled studies) did not demonstrate difference in mortality between colistin alone and colistin–carbapenem combination therapy for the treatment of carbapenemase-producing GNB or carbapenem-resistant GNR [270].

Two randomized controlled studies are currently recruiting patients, comparing colistin–carbapenem combination therapy versus colistin monotherapy for invasive infections caused by MDR and XDR-GNB, will clarify this issue (NCT01732250, NCT01597973).

Aerosolized colistin can be considered as an adjunctive therapy for MDR infections causing pneumonia. A successful use of 100–150 mg colistin, administered via a Respirgard II nebulizer, as part of combination therapy for nosocomial pneumonia caused by MDR *Pseudomonas aeruginosa* was described [271]. Potential concerns over aerosolized colistin include development of resistance to the antibiotic [272]. In a retrospective study which compared treatment of colistin-only susceptible GNR bacteria with intravenous (IV) colistin vs. aerosolized colistin in adjunction to IV colistin, patients who received the adjunction therapy had a higher clinical cure rate required fewer days of mechanical ventilation after VAP onset [225].

21.5 Prevention

A meta-analysis of 109 trials performed during 1973–2010 reported that antibiotic prophylaxis, especially with quinolones, in afebrile neutropenic patients significantly reduced all-cause mortality [273]. Antibacterial prophylaxis with a fluoroquinolone (levofloxacin or ciprofloxacin) to prevent bacterial infections was recommended for adult SCT patients with anticipated neutropenic periods of 7 days or more. Antibacterial prophylaxis is generally started at the time of stem cell infusion and continued until recovery from neutropenia or initiation of empirical antibacterial therapy for fever during neutropenia. The prophylaxis should not be continued after recovery from neutropenia. Quinolone prophylaxis, however, has to be reconsidered in the situation of growing resistance. Local epidemiological data should be carefully considered before applying fluoroquinolone prophylaxis and once it is applied, the emergence of resistance in bacterial pathogens should be monitored closely because of increasing quinolone resistance worldwide [54]. Prophylaxis efficacy may be reduced when the prevalence of fluoroquinolone GNR bacillary resistance exceeds 20 % [274, 275]. Although a meta-analysis of 27 studies, published at 2007, reported on nonsignificant increase in colonization by quinolone-resistant bacteria under quinolone prophylaxis [276], later studies reported that infections which emerge under quinolone prophylaxis can be caused by MDR bacteria, necessitating use of broader spectrum antibiotics for treatment [277, 278]. Possible benefit of quinolone prophylaxis has to be considered based on local epidemiology and resistant data and if prophylaxis is discontinued—outcome of bacterial infections has to be closely monitored.

21.5.1 Prevention of Resistance

Efforts to reduce antibiotic resistance among transplant patients must address two directions: limitation of use of broad spectrum antibiotics and disruption of spread of resistant bacteria.

Heavy antibiotic use has been constantly reported as one of the main factors for development of resistant bacteria. Limitation of unnecessary use of broad spectrum antibiotics is important to reduce the spread of resistance.

The ECIL group has proposed guidelines for empirical antibiotic therapy in the era of growing resistance [279]. Initial antibiotic regimen has to be targeted on the most prevalent bacteria at the center, unless the patient is seriously ill at presentation or is known to be colonized or previously infected with resistant bacteria. Differential approaches should be implemented for febrile neutropenic patients based on their presentation, knowledge on colonization/previous infection with resistant bacteria and local epidemiology in each center. An escalation strategy is recommended for patients with uncomplicated presentation, who are unknown to be colonized or previously infected with resistant bacteria, in centers where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia. Such patients should be treated empirically with either anti-pseudomonal cephalosporins (cefepime, ceftazidime), or beta lactam-beta lactamase inhibitors (piperacillin–tazobactam, ticarcillin–clavulanate, cefoperazone–sulbactam) or combination of piperacillin and gentamicin. Usage of carbapenems and combinations should be avoided in such patients. Modifications of the initial regimen at 72–96 h should be based on the patient's clinical course and the microbiological results. The ECIL guidelines defined situations in which use of carbapenems and combination therapy is justified (de-escalation approach), specifically in seriously ill patients, e.g., presentation with septic shock; those known to be colonized or previously infected with resistant bacteria or in centers with a high prevalence of infections due to resistant bacteria at the onset of febrile neutropenia. This de-escalation approach has to be followed by discontinuation of combination therapy or switch to a narrower-spectrum regimen in patients who were stable since presentation and in whom resistant bacteria was not isolated, especially if fever normalized.

The empirical antibacterial treatment can be discontinued at ≥72 h irrespective of neutrophil count or expected duration of neutropenia in patients without evidence of clinically or microbiologically documented infections, who are hemodynamically stable since presentation and afebrile ≥48 h [280]. The patient should be kept hospitalized for at least 24–48 h under close observation if he is still neutropenic when antibiotic therapy is stopped. If fever recurs, antibiotics should be restarted urgently. This strategy aims to limit exposure to broad spectrum antibiotics and combinations, and also duration of antibiotic treatment, minimizing the collateral damage associated with antibiotic overuse, and the further selection of resistance.

Promising new diagnostic techniques enabling rapid (within few hours) identification of ESBL and carbapenemase-producing bacteria, with high sensitivity and specificity, may contribute to avoid of overuse of carbapenems [281–283]. The problem is that these tests should be applied on positive blood cultures, meaning that still ~24 h (ideally) will pass from the onset of infection until the result of these tests will be available. These tests can miss some carbapenemases in some bacteria (e.g., OXA-48, *Pseudomonas aeruginosa*) and they do not detect carbapenem-resistant bacteria due to mechanisms other than carbapenemases (e.g., reduced permeability of the outer membrane associated with overexpression of chromosomal or acquired AmpC and/or ESBL [284–286].

Antibiotic stewardship is crucial to use antimicrobials in such a way that each and every patient receives the most efficacious and safe antimicrobials to treat their infections, while at the same time minimizing the ecologic impact of

antimicrobials used [287]. Five main principles of antibiotic stewardship in HSCT patients were defined [288]:

1. Local surveillance of antibiotic resistance, antibiotic consumption and patient outcomes, including monitoring reports;
2. Multidisciplinary protocols and algorithms on the diagnosis, prevention and treatment of infections should be developed in collaboration of oncologists, infectious disease specialists, and medical microbiologists and updated to reflect changes in bacterial antimicrobial susceptibilities in the unit;
3. Swift reporting of positive clinical cultures and implementation of rapid techniques for bacterial identification and resistance patterns by the microbiology laboratory to control the duration of treatment and to facilitate reassessment of the antibiotic therapy;
4. Optimization of dosing regimens using pharmacodynamic principles;
5. Frequent multidisciplinary rounds including discussion of patient histories and interactive, bedside education on antimicrobial drug use and infection control.

Infectious control is crucial to prevent spread of resistant bacteria between patients within department, as well as between departments in the hospital and between hospitals. Antimicrobial resistance is a worldwide problem. Transportation of patients between departments in the same hospital, as ICU, surgery and transplant ward, between different hospitals, as well as medical tourism, contributes to the spread of resistant bacteria across the borders. Horizontal transmission of ESBL-producing *Klebsiella*, from patient to patient, via the hands of staff members has been very well documented [289–291]. Interventions to prevent and control the spread of MDR bacteria include hand-hygiene measures; active screening of patients with cultures; contact barrier precautions; enforcement of isolation criteria for patients colonized or infected with multidrug-resistant organisms; the use of single rooms for HSCT recipients; cohorting of infected patients; environmental cleaning and anti-infective stewardship [288, 292, 293]. Bundles including combination of multiple interventions were efficient for containment of carbapenem-resistant Enterobacteriaceae [99, 291]. Avoidance of contact with resistant *Pseudomonas* infected patients is important to prevent MDR *Pseudomonas* acquisition in lung transplant recipients [194].

Rapid detection and isolation of patients colonized with resistant bacteria can limit its spread. Novel molecular-based diagnostic screening tests enable simultaneous detection of several resistant bacteria directly from swab samples with high sensitivity, specificity, positive predictive value, and negative predictive value and results available in 24 h [294, 295].

Decolonization of patients colonized with CRE with oral aminoglycoside or colistin was successful in 37–68 % of patients, although the appropriate dose has to be determined and there is concern that those who remained colonized will be colonized with resistant bacteria after de-colonization [296–301].

Transmission of microorganisms from an infected brain-dead donor can cause severe, sometimes fatal infection in the SOT recipient, even if appropriate therapy is provided [115, 302, 303]. On the other hand, the donor pool is limited and increasing numbers of donors have underlying diseases, and may be infected with MDR bacteria. Investigation of donors for CRE carriage by suitable approaches (e.g., rectal swabbing) would seem mandatory, especially in areas where CRE are endemic [302]. A systematic approach for the acceptability of organs from donors infected with MDR bacteria was suggested, based on expert opinion [304]. The algorithm includes screening for MDR GNR in potential donors, who are at risk for MDR infection. If a donor was found to be colonized/infected with MDR bacteria, prophylactic antibiotic treatment should be initiated to donor and to recipient, with the appropriate agent according to susceptibility testing. Two conditions are contraindication to SOT: (1) if the donor has MDR bacteremia (2) lung transplantation from donor infected/colonized with MDR bacteria for which no adequate antibiotic treatment for pneumonia exists [304].

21.6 Summary

Infections caused by GNR are increasingly common in transplant recipients; they can cause severe, life-threatening diseases. Prevention approaches, early diagnosis, appropriate empiric therapy based on local epidemiology and proper targeted therapy are crucial for patients survival. There is a global problem of growing resistance among GNR and it compromises prophylaxis and treatment options. Previous colonization and exposure to antibiotics are the most important risk factors for the development of resistance. Treatment of carbapenem-resistant GNR is challenging; in some cases, the only treatment options include old antibiotics (polymyxins and fosfomycin), tigecycline, and aminoglycosides. All these options have efficacy, resistance, and/or toxicity issues. Development of new treatment modalities is an important goal. Continuous monitoring of the local epidemiology and antimicrobial stewardship is mandatory for optimization therapy with the currently available drugs. Infectious control is crucial to limit the spread of resistance.

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