Gram-Negative Infections

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12.1 Epidemiology of Gram-Negative Bacterial Infections in Haematology Patients

During the last 50 years, two major shifts could be noticed in the epidemiology of bacteria causative for infections and particularly bloodstream infections in febrile neutropenic cancer patients. Until the mid-1980s, gram-negative bacteria, particularly *Escherichia coli* and *Pseudomonas aeruginosa*, were the main infectious agents in these patients. Then, presumably due to the increased use of high-intensity chemotherapeutic regimens leading to a higher incidence of severe mucositis, the frequent use of fluoroquinolone (FQ) prophylaxis and indwelling long-term vascular catheters, gram-positive bacteria, particularly coagulase-negative staphylococci and viridans streptococci, became the dominant infecting agents.

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Since the turn of the twenty-first century, gram-negative bacteria have re-emerged in many haematology centres throughout the world (Gustinetti and Mikulska 2016). However, the main difference between gram-negative bacteria in 2000s and those in 1970s and 1980s is the significant antimicrobial resistance in the former, which causes a severe compromise in patients with acute leukaemia (AL) and other haematological malignancies and in those undergoing haematopoietic stem cell transplantation (HSCT) (Akova 2016). Currently, enteric gram negatives (particularly *E. coli* and *Klebsiella pneumoniae*) and non-fermentative bacteria (*P. aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*) are primarily responsible for gram-negative bloodstream infections (BSIs) in febrile neutropenic cancer patients (Alp and Akova 2013; Kara et al. 2015). Since multidrug resistance (MDR) is a common problem among these pathogens, empirical therapy in febrile neutropenic cancer patients may need to be devised accordingly. However, most of the current guidelines do not recommend empirical regimens for these highly resistant bacteria. This may delay antibiotic therapy (Freifeld et al. 2010; Averbuch et al. 2013). Current standard microbiological techniques do not allow identification of both bacteria and antimicrobial resistance earlier than within 36–48 h, thus delaying appropriate antibiotic therapy (Kirn and Weinstein 2013).

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12.1.1 Mechanisms of Emerging Antimicrobial Resistance in Gram-Negative Bacteria

The main resistance mechanism of MDR in gram-negative bacilli is the production of various beta-lactamase enzymes including extended-spectrum beta-lactamases (ESBLs) and carbapenemases (Alp and Akova 2017). The latter enzymes are encoded by multicopy plasmids in these bacteria. These plasmids often also carry resistance determinants for other antibiotics, thus leading to multi- or extended-drug resistance (MDR, XDR phenotypes) (Magiorakos et al. 2012). Other mechanisms contributing to resistant phenotypes are porin mutations, efflux pumps and target modifications. Usually, two or more of these mechanisms can be found simultaneously in the same strain (Eichenberger and Thaden 2019).

12.1.2 Carbapenem and Extended-Spectrum Cephalosporin-Resistant Enterobacteriaceae

Extended-spectrum beta-lactamases, especially the CTX-M type, confer resistance against broad-spectrum cephalosporins and penicillins, particularly in *E. coli*, but also in other members of Enterobacteriaceae. ESBL-encoding plasmids may also encode resistance to aminoglycosides, tetracyclines, sulphonamides and trimethoprim. These plasmids frequently encode an inhibitor-resistant beta-lactamase, namely OXA-1, which provides resistance to beta-lactamase inhibitors including amoxicillin/clavulanate and piperacillin/tazobactam (Livermore 2012). One of the new beta-lactamase inhibitor combinations, namely ceftolozane/tazobactam, may overcome this resistance, since ceftolozane is resistant to hydrolysis by OXA-1 (Zhanel et al. 2014). *Escherichia coli* sequence type ST131 with CTX-M-15 ESBL production is emerging worldwide and has a high epidemic potential.

Carbapenem resistance (CR) may occur due to the production of various carbapenemases, expression of efflux pumps, porin mutations, or combination of these mechanisms (Eichenberger and Thaden 2019). Three different types of carbapenemases are usually accounted for CR in most of the carbapenem-resistant Enterobacteriaceae (CRE): *Klebsiella pneumoniae* carbapenemase (KPC), an Ambler Class A enzyme (Ambler 1980), is highly prevalent in the United States, Western Europe and South East Asia. The KPC gene is located on a plasmid that can be transferred between species. KPC can hydrolyse and thereby inactivate almost all penicillins, cephalosporins and aztreonam along with carbapenems, but most of the new beta-lactam/beta-lactamase inhibitor combinations can inhibit KPC. The most common Class D beta-lactamases in Enterobacteriaceae are OXA-48-like enzymes (Mairi et al. 2018). These enzymes are weak carbapenemases; thus, the bacteria usually remain susceptible to broad-spectrum cephalosporins. However, Enterobacteriaceae harbouring these enzymes often additionally carry an ESBL gene that provides resistance to cephalosporins. OXA-48-producing *K. pneumoniae* was first described in Turkey in 2001 and has been spread to Europe, North Africa, the Middle East and India. These enzymes are rarely encountered in the United States and South East Asia. Metallo-beta-lactamases (MBLs) are Class B carbapenemases and can hydrolyse all beta-lactams except aztreonam. Unfortunately, none of the new beta-lactamase inhibitors is active against the new classes of carbapenemases. Two new agents, namely aztreonam/avibactam and cefiderocol, which are currently being evaluated in Phase 3 trials, show a strong in vitro activity and may be useful against MBL-producing Enterobacteriaceae (Theuretzbacher et al. 2019). New Delhi metallo (NDM-type) enzymes are the most prevalent enzymes in this group and are endemic in the Indian subcontinent. They have also been found in the European continent, but are less frequent in Americas (Eichenberger and Thaden 2019). Verona integron-encoded metallo-beta-lactamase (VIM) is another metalloenzyme that has chemical characteristics similar to those of NDM enzymes. VIM is frequently reported in non-enteric gram-negative bacteria. Enterobacteriaceae with VIM production are

usually found in Southern European countries (Matsumura et al. 2017).

When compared with *K. pneumoniae*, the production of carbapenemases and CR are lower in *E. coli* (Poirel et al. 2018). Like ESBL-producing strains, carbapenem-resistant strains of Enterobacteriaceae frequently acquire resistance to other classes of antibiotics, including aminoglycosides, FQs, tetracyclines and trimethoprim–sulfamethoxazole (TMP-SMX) by various mechanisms.

Although polymyxins have usually been active against these XDR pathogens, the emergence of colistin resistance has become widespread in certain locations (Jeannot et al. 2017). Resistance to polymyxins typically results from chromosomally determined lipopolysaccharide modifications; however, a plasmid-mediated resistance has also been described. The latter type of resistance was recently reported in *E. coli* from faecal samples collected from three patients with acute leukaemia (Lalaoui et al. 2019).

Extensively drug-resistant (XDR) *Pseudomonas aeruginosa*: Loss of porins and presence of efflux pumps (such as MexA-MexB-OprM) can cause intrinsic resistance to several antibiotics, including rifampin plus TMP-SMX, tetracycline and most beta-lactam antibiotics, including carbapenems, in *P. aeruginosa* (Eichenberger and Thaden 2019). The porin protein OprD allows carbapenem uptake through the outer membrane. Loss of this protein confers resistance to imipenem and reduced susceptibility to meropenem. When OprD loss is combined with upregulated MexA-MexB-OprM, *P. aeruginosa* gains an XDR phenotype that is resistant to almost all beta-lactams, quinolones and tetracyclines.

P. aeruginosa intrinsically possesses Class C chromosomal beta-lactamases (AmpC). Mutations can lead to hyperproduction (derepressed state) of these enzymes which results in resistance to all broad-spectrum cephalosporins, penicillins and aztreonam. Additional acquisition of plasmid-mediated broad-spectrum beta-lactamases (such as PER-1, VEB-1, GES-1 and some OXA-type enzymes) enhances resistance to all beta-lactams except carbapenems. The latter can be hydrolysed by acquired MBLs including VIM, IMP, SMP and GIM.

Aminoglycoside-modifying enzymes are also encoded on transferable plasmids and confer resistance to aminoglycosides. Mutations in FQ targets such as *parC* and gyrA can lead and augment quinolone resistance in addition to that conferred by efflux pumps. Several clones exert an XDR phenotype, and the globally most frequent clone is ST235, which may have 39 different beta-lactamases from Class A (PER-1, GES), Class B (VIM) and Class D (OXA type) enzymes (Eichenberger and Thaden 2019).

Extensively drug-resistant (XDR) *Acinetobacter baumannii*: This microorganism has similar mechanisms of antibiotic resistance as described for *P. aeruginosa*. CR is the hallmark of an XDR phenotype. EARS-Net surveillance by ECDC reported prevalence of CR in *A. baumannii* in the EU at 49% (European Centre for Disease Prevention and Control 2019). This figure may be up to >90% in South East Asia and South America. A hyperexpressed adeABC efflux pump combined with OXA-type carbapenemases (OXA-23, 40 and 58-like enzymes) leads to high-level CR (Akova 2016).

12.1.3 Current Epidemiological Figures and Emerging Threat of Resistant Gram-Negative Bacilli

Since the turn of the twenty-first century, gram-negative bacteria with various antibiotic resistance patterns have become the dominating life-threatening microorganisms in patients with haematological malignancies. A multicentre survey by the European Conference on Infections in Acute Leukaemia (ECIL-4) from 39 centres in 18 countries from Europe and Near East in 2011 revealed a reduction of the gram-positive to gram-negative ratio when compared with previously published literature (55%:45% vs. 60%:40%, respectively) (Mikulska et al. 2014). The rate of Enterobacteriaceae has increased (30% vs. 24%, respectively), whereas the rates of *P. aeruginosa*

has declined (5% vs. 14%). One particular finding in this survey is that, although overall resistance rates were lower than those already published, South-Eastern European countries have a significantly higher frequency of resistance compared to those in North-Western Europe. The north to the south shift in Europe in antimicrobial resistance has been significant over the years, and recently, a complex scheme of contributing factors has been described that goes beyond antimicrobial usage (Collignon et al. 2018).

Similar observations were reported in a recent European Society for Blood and Marrow Transplantation (EBMT) survey with HSCT recipients (Averbuch et al. 2017). Sixty-five HSCT centres from Europe, Asia and Australia reported data on 591 patients with 655 gram-negative BSI episodes caused by 704 pathogens. Enterobacteriaceae accounted for 73% of all episodes and non-fermentative bacteria for 24%. FQ resistance was present in 50.4% of all isolates, non-carbapenem beta-lactam resistance in 50.9%, CR in 18.5% and MDR in 35.2%. *Klebsiella pneumoniae* isolates had the highest rate of CR (25%), whereas this figure was low in non-Klebsiella Enterobacteriaceae (2.3% in *E. coli*, 7.3% in *Enterobacter* spp.). *Acinetobacter baumannii* was resistant to carbapenems in 63.6% of the isolates and *P. aeruginosa* in 37.9%. In centres where FQ prophylaxis was provided, higher rates of FQ resistance in gram negatives were observed (79% vs. 50%, p = 0.001). Patients with allogeneic HSCT (allo-HSCT) showed higher resistance rates, and similar to the previous report by Mikulska et al. (Mikulska et al. 2014), higher resistance rates were shown in South East vs. North East Europe.

A sevenfold increase in carbapenem-resistant *K. pneumoniae* isolates from BSIs among HSCT recipients was reported between 2010 and 2013 in 52 Italian centres (Girmenia et al. 2015). Another prospective Italian study with 2743 HSCT patients reported a cumulative incidence for gram-negative BSIs of 17.3% and 9% in the pre-engraftment period of allo- and auto-HSCT (Girmenia et al. 2017). *Escherichia coli* was the most frequent pathogen, followed by *K. pneumoniae* and *P. aeruginosa* in both allo- and auto-HSCT.

A total of 2388 HSCT patients with neutropenia (61.6% with allo-HSCT) were analysed in a prospective, multicentre study in 20 HSCT centres from Germany, Austria and Switzerland between 2002 and 2014. The incidence of BSIs did not change over the study period (15.8%). Although gram-positive bacteria were predominating agents of BSIs (63.9%), the incidence of gram-negative BSIs increased in both allo-HSCT patients (1.4% in 2002 vs. 6.4% in 2014, $p < 0.001$) and auto-HSCT patients (3.6% in 2002 vs. 7.4% in 2014, $p = 0.001$). *Escherichia coli* was the leading pathogen (19.9% of all BSIs) for which the incidence increased threefold in allo-HSCT patients. Overall, 11% of Enterobacteriaceae from BSIs produced ESBL, and no significant increase in this pattern occurred during the study period.

A recent systematic review and meta-analysis of 22 studies between 1998 and 2014 with 5650 BSI patients with cancer reported a pooled prevalence of 11% of ESBL production among Enterobacteriaceae in patients with haematological malignancy (Alevizakos et al. 2017). Stratification according to geographic region indicated pooled prevalence figures of 7% in Europe (Turkey, Italy, Germany, Sweden and Spain), Eastern Mediterranean region (Saudi Arabia, Jordan) and South America (Brazil); 10% in Western Pacific region (China, Malaysia, South Korea, Hong Kong); and 30% in South East Asia (India). In addition, an annual increase of 7.1% in the production of ESBL in enteric gram negatives was observed.

Beyond multicentre analysis, single-centre data have shown greater variations both in epidemiology and in antibacterial resistance. Bodro et al. (Bodro et al. 2014) reported on 1148 bacteraemia episodes in adult cancer patients (58% with haematological malignancies) between 2006 and 2011. ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, K. pneumoniae*, and *P. aeruginosa* and *Enterobacter* spp.) caused bacteraemia in 392 episodes (34%). In 54 episodes (4.7%), resistant ESKAPE pathogens were isolated: 33.3% carbapenem- and quinolone-

resistant *P. aeruginosa*, 22.2% stably derepressed and ESBL-producing *Enterobacter cloacae*, 13% ESBL-producing *K. pneumoniae* and 7.4% carbapenem-resistant *A. baumannii*.

Between 2005 and 2009, 3703 neutropenic episodes in 2098 patients with haematological malignancies were analysed in a large tertiary care centre in Turkey (Kara et al. 2015). The frequency of BSIs was 14.5%. Among them, gram-negative pathogens were the predominant bacteria (52.6%). *Escherichia coli* (17.3%), *Klebsiella* spp. (11%), *Acinetobacter* spp. (7.1%) and *P. aeruginosa* (6.7%) were the most frequently isolated bacteria. Extended-spectrum beta-lactamase production was 45% in *E. coli* and 23% in *Klebsiella* spp. and did not change much during the study period. Overall FQ resistance was 33.3% in gram-negative bacteria, ceftazidime resistance was 28% in *P. aeruginosa*, and MDR pattern was found 87% in *A. baumannii.* Meropenem resistance was observed in 11.5% of all gram-negative bacteria in high-risk haematology patients (i.e. acute leukaemia and HSCT recipients), 10% in *K. pneumoniae*, 20% in *P. aeruginosa* and 35.3% in *Acinetobacter* spp. No CR was in found in *E. coli*. A follow-up surveillance in 153 patients with 254 BSI isolates revealed ESBL production in 41.9% of *E. coli* and 42.6% of *K. pneumoniae* and CR was present in 5.1% of *E. coli* and in 44.2% of *K. pneumoniae* (a > fourfold increase over the previous period) and in all *A. baumannii* isolates (Ayaz et al. 2018).

A total of 2083 patients with haematological malignancy were retrospectively evaluated in a Taiwanese hospital between 2008 and 2013 (Chen et al. 2017). Lymphoma was the most common underlying disease (38.1%), closely followed by acute myeloid leukaemia (30.9%). Gram-negative bacteria were the leading cause (53.7%) of bacteraemia among 1310 non-duplicate isolates in neutropenic patients. The isolates included *E. coli* (13.8%), *K. pneumoniae* (9.5%), *A. calcoaceticus–baumannii* (ACB) complex (5.7%) and *P. aeruginosa* (4.0%). MDR was detected in 21.8% of the ACB complex isolates. Comparing the distribution of resistant bacteria in three different periods (1995–2011, 2002–2006 and 2008–2013), the investigators detected significant increases in rates of cefotaxime-resistant *E. coli*, and CR rates in *E. coli*, *P. aeruginosa* and ACB complex isolates.

Varying incidences up to 32% of polymicrobial BSIs have been reported for all episodes of BSIs (Rolston et al. 2007). However, more recent series noted an incidence of around 10% with a dominance of resistant gram-negative bacteria as the causative agents (Royo-Cebrecos et al. 2017).

Analysis of the so-called blood microbiome by high-throughput sequencing (HTS) method in neutropenic cancer patients can lead to the identification of non-culturable microorganisms (Gyarmati et al. 2015; Gyarmati et al. 2016; Horiba et al. 2018). In a study with 130 blood samples in 33 patients, 98% of the identified reads by HTS were known human pathogens and 65% of them belonged to the normal human gut microbiota, confirming that a translocation from the gut has a critical role in the pathogenesis of BSIs in neutropenic patients (Gyarmati et al. 2015; Song and Peter 2019). While only bacteria belonging to *Firmicutes* phylum were isolated with blood cultures, 5 phyla and 30 genera mostly belonging to anaerobic and facultative genera were identified with HTS. Although the importance of this finding is yet to be determined in larger series, one point deserves to be mentioned: The *Shewanella* genus (formerly classified as *Pseudomonas*) was detected in over 80% of the samples analysed by HTS. The authors suggested that its relevance might have been underestimated since these bacteria are not routinely diagnosed. Although preliminary, these findings may explain why most neutropenic patients with fever of unknown origin (i.e. those with negative blood cultures) respond to initial empirical antibacterial therapy.

12.1.4 Risk Factors for Gram-Negative Infections and Related Mortality

Several risk factors have been described for severe, antibiotic-resistant gram-negative bacterial sepsis and the related mortality in neutropenic, haemato-

Table 12.1 Factors facilitating gram-negative bacterial sepsis in HSCT recipients

Age of the recipient
Severity of immunosuppression and neutropenia
Comorbidities and organ dysfunctions
Type of HSCT transplantation (Allo- vs. auto-transplantation)
Degree of stem cell match (full matched, mismatched, haploidentical)
Mucosal injury
Central venous catheter
Previous exposure to antimicrobials (such as fluoroquinolone prophylaxis)
Change in host microbiota
Previous colonisation by resistant gram negatives
Presence of acute or chronic graft versus host disease (GVHD)

logical cancer patients. In HSCT transplant patients, a complex interplay between various host and graft factors may predispose patients to have serious gram-negative infections. Table 12.1 summarises the most important predisposing factors to gram-negative bacteraemia and related mortality in haematological cancer patients.

The relationship between severity and longevity of neutropenia and gram-negative bacteraemia has long been known (Gustinetti and Mikulska 2016; Akova 2016). Previous antibiotic exposure may lead to gram-negative colonisation. Then, these bacteria can translocate from the gut through the chemotherapy-disrupted mucosa, leading to bacteraemia (Song and Peter 2019). However, a recent literature review of FQ prophylaxis in neutropenic patients and a large surveillance study identified conflicting results on colonisation or infection with MDR strains after prophylaxis (Mikulska et al. 2018a; Kern et al. 2018).

In a multicentre, prospective observational study with 2226 admissions in 18 haematological institutions in Italy revealed that 144 patients (6.5%) were colonised with MDR gram negatives at admission (Cattaneo et al. 2018). ESBL-producing bacteria were found in 44% of the colonised patients and CRE was found in 59%. Overall, 25.7% of the colonised patients developed at least one episode of BSI. In 62.2% of the BSIs, previously colonised bacteria were the responsible agents. Overall survival at 3 months was significantly lower in CRE-colonised patients (83.6%) as compared with ESBL colonisers (96.8%). In another multicentre trial, a total of 278 episodes of *K. pneumoniae* BSI was analysed between 2010 and 2014 (Trecarichi et al. 2016). CR was present in 57.9% of the isolates. Overall 21-day mortality was 36.3%. Factors related to mortality were septic shock, acute respiratory failure, inadequate antimicrobial therapy and CR (Trecarichi et al. 2016). In a retrospective survey involving 52 centres in Italy, carbapenem-resistant *K. pneumoniae* (CRKp) colonisation before or after transplant was followed by infection in 25.8% and 39.2% of auto- and allo-HSCT recipients, respectively (Girmenia et al. 2015). The infection-related mortality rates were 16% and 64.4% in respective recipients. Multivariate analyses revealed that CRKp infection before transplantation and subsequent CRKp-targeted first-line antibiotic therapy were significantly related with mortality due to infection after allo-HSCT. A global prevalence study and systematic review also indicated that CR in gram negatives infecting neutropenic patients is correlated with mortality and previous exposure to carbapenems (Righi et al. 2017).

MDR *P. aeruginosa* was identified in 7% of 589 episodes of BSIs in 357 acute leukaemia cases. The related factors for MDR phenotype were found to be prior anti-pseudomonal cephalosporin and current beta-lactam use, shock and pulmonary source of infection. Inappropriate treatment of BSIs caused by this pathogen was significantly associated with mortality in patients (Garcia-Vidal et al. 2018).

The type of HSCT may affect the frequency and severity of gram-negative BSIs. Due to the higher intensity of immunosuppression, allo-HSCT recipients are more prone to severe infections and increased mortality than auto-HSCT recipients. In a single-centre study in China, 1847 patients undergoing haploidentical or human leukocyte antigen (HLA)-identical sibling HSCTs between 2013 and 2016 were analysed (Yan et al. 2018). Haploidentical transplant recipients had more and earlier BSIs than HLA-identical transplant recipients. A multivariate

analysis revealed that diagnosis of myelodysplastic syndrome, interval from diagnosis to HSCT >190 days, carbapenem therapy and grade 3–4 mucositis were related with the occurrence of BSI, mostly by *E. coli* and *K. pneumoniae* as gram-negative pathogens. BSI was an independent risk factor for an increased all-cause mortality in haploidentical recipients at 3 months.

12.2 Emerging Issues in the Diagnosis of Gram-Negative Infections

Blood cultures are still considered the gold standard for diagnosing BSIs (Kirn and Weinstein 2013). However, only 10–30% of blood cultures are positive in febrile neutropenic patients (Gyarmati et al. 2015). With modern automated systems, time-to-culture positivity could be less than 24 h for most of the MDR pathogens (Puerta-Alcalde et al. 2019), but antibiotic susceptibility test results may take another 7–24 h even with the most advanced automatisation (Marschal 2017). When one considers the consequences of inappropriate empirical antimicrobial therapy in neutropenic cancer patients, this lag time is too long. Thus, the current interest in developing point-of-care tests for bedside identification of the causative microorganisms and their resistance mechanisms is very high. Multiplex polymerase chain reaction (PCR) methodology can identify multiple bacterial species simultaneously, and several commercial tests are available (Lebovitz and Burbelo 2013). However, with these tests, only a limited of number of bacteria can be identified. Species identification with matrix-assisted laser desorption ionisation–time of flight (MALDI-TOF) mass spectrometry and molecular techniques have been used in combination to shorten the time to diagnosis, aiming for earlier appropriate antimicrobial therapy (Egli et al. 2015; de Souza et al. 2018). Combining MALDI-TOF identification with real-time antimicrobial stewardship intervention has been shown to shorten the time to appropriate antibiotic therapy (Beganovic et al. 2017). The 16S metagenomics sequencing library can be used to detect bacteria simultaneously in blood samples. It is based on PCR amplification of the 16S ribosomal RNA gene and subsequent sequencing of the amplicons. This gene is highly conserved in prokaryotes but not present in humans (Rutanga et al. 2018). By combining these methods, not only bacterial pathogens can be identified but also information about their antimicrobial resistance mechanisms can be obtained. In a few small-scale trials, several uncultured bacteria could be identified in blood samples from neutropenic patients. However, these techniques still require ample time for positive results and are no point-of-care tests. Nonetheless, identifying several bacterial phyla in a patient with neutropenia without fever may help to predict future bacteraemia episodes and may lead to a tailored empirical antimicrobial therapy. An extensive review on the diagnosis of BSIs from positive blood cultures and directly from blood samples was recently published (Peker et al. 2018).

12.3 Current Approaches for Empirical Therapy of Gram-Negative Bacteria: Escalation and De-Escalation Therapy

The choice of effective antimicrobial therapy among haematological patients is hampered by an increased number of gram-negative bacteria (GNB) that re-emerged as the most common pathogen isolated from blood cultures along with high resistance rates to broad-spectrum antibiotics (Montassier et al., 2013; Gudiol et al., 2013; Rolston, 2005). Most commonly isolated GNBs include Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and, less frequently, *Acinetobacter* spp. (Klastersky et al., 2007). In areas where antimicrobial resistance in GNB is common, the correct choice of empirical therapy is particularly challenging, especially among patients with severe infections that require prompt treatment. MDR pathogens responsible for life-threatening infections among haematological patients include

extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and carbapenem-resistant bacteria (e.g. *A. baumannii*, *K. pneumoniae* and *P. aeruginosa*) (Satlin et al., 2013). Among neutropenic patients, infections caused by carbapenem-resistant bacteria have been associated with increased mortality (Righi et al., 2017). Various risk factors have been associated with the development of MDR GNB infection, including advanced underlying disease with severe clinical presentation, prolonged hospital stay, colonisation or previous infections with resistant bacteria, exposure to broad-spectrum antibiotics and urinary catheter placement (Sahin et al., 2009; Gudiol et al., 2011; Gudiol et al., 2010; Kang et al., 2012). The use of inadequate antimicrobial regimens due to the presence of MDR bacteria is a frequent cause of delayed initiation of appropriate treatment and represents one of the main causes for adverse outcomes in patients with severe infections, especially among those with profound immunosuppression (Cosgrove, 2006; Ramphal, 2004). The correct approach to severe infections in haematological patients is based on the assessment of various factors, including patient's characteristics (e.g. age, duration of aplasia, liver and/or kidney impairment, history of previous infections or colonisation due to MDR GNB), infection characteristics (e.g. type of infection and disease severity), as well as the site's local epidemiology and resistance patterns. Prompt initiation of appropriate empiric therapy is paramount in haematological patients, and should be followed by clinical reassessment after the availability of susceptibility tests (Bassetti & Righi, 2013). Finally, the choice of a correct targeted therapy should take the patient's comorbidities, type and site of the infection, and pathogen resistances into account (Averbuch et al., 2013).

According to these factors, an 'escalation' or a 'de-escalation' approach can be selected to treat severe infections in haematological patients (Table 12.2). Escalation therapy usually includes coverage against non-resistant Enterobacteriaceae and *P. aeruginosa*, using monotherapy with a beta-lactam (e.g. ceftazidime, cefepime or piperacillin/tazobactam). This approach reduces the use of carbapenems and combination treatment, thus limiting toxicities and selection pressure, and can be modified in case of clinical deterioration or isolation of a resistant pathogen. In case of compromised patients with severe presentation or risk for infections caused by MDR GNB (e.g. high local prevalence of ESBL-producing bacteria, previous history of colonisation or infection due to MDR GNB, or other risk factors for resistance), a strategy using a narrow-spectrum antibiotic may lead to inadequate early treatment and potential negative outcomes. In these cases, a de-escalation therapy using broad-spectrum regimens (e.g. a carbapenem or combination therapy with an aminoglycoside plus a beta-lactam, or colistin with a beta-lactam) that are active against highly resistant pathogens is recommended. De-escalation therapy should always be followed

Table 12.2 Escalation and de-escalation approaches in the treatment of infections among patients with haematological malignancies

Escalation approach	
Indication	Antimicrobial therapy
• Sites where infections due to MDR bacteria are rare, and strict surveillance system is in place. • Uncomplicated clinical presentation. • No known colonisation with MDR bacteria. • No previous infection with MDR bacteria.	• Anti-pseudomonal cephalosporin (e.g. cefepime, ceftazidime). • Piperacillin/tazobactam.
De-escalation approach	
• ESBL prevalence is high or MDR pathogens are regularly seen. • Known colonisation or previous infection with ESBL-producing or other resistant GNB. • Previous exposure (<30 days) to broad-spectrum antibiotics. • Seriously ill patients (e.g. septic shock, pneumonia) .	• Carbapenem monotherapy. • Anti-pseudomonal beta-lactam + aminoglycoside or fluoroquinolone. • Colistin + beta-lactam. • Early coverage of MDR gram-positive bacteria .

MDR, multidrug-resistant; *ESBL*, extended-spectrum beta-lactamase; *GNB*, gram-negative bacteria

by clinical reassessment after 48–72 h of treatment to optimise antimicrobial therapy according to the results of susceptibility tests.

In conclusion, MDR GNB threat should be taken into consideration when choosing an empirical treatment for haematological patients, according to clinical parameters and the local epidemiology. Prompt patient evaluation, risk assessment and treatment with broad-spectrum antibiotics are required when MDR GNB involvement is suspected. Reassessment after 48–72 h from the beginning of an empiric treatment is mandatory to optimise a targeted therapy, in case of documented multiple resistances, and to avoid an unnecessary use of broad-spectrum antibiotics. Implementation and review of infection control policies are mandatory if MDR pathogens are regularly seen at the onset of febrile neutropenia.

12.4 New Antimicrobial Options for the Treatment of MDR Gram-Negative Infections

The emergence of MDR GNB strains, including MDR *P. aeruginosa* and extended-spectrum beta-lactamases (ESBLs)-producing Enterobacteriaceae, has dramatically narrowed the choices for targeted treatment and increased the risk of empirical inadequate therapy (Kanj & Kanafani, 2011). Furthermore, the increased use of broad-spectrum antimicrobials led to the emergence of isolates that were resistant to the majority of available molecules, including carbapenems and colistin (Gupta et al., 2011; Munoz-Price et al., 2013; Liu et al., 2016).

In the past decades, the increase in MDR GNB has not been counterbalanced by the availability of new compounds (Hersh et al., 2012). Fortunately, new molecules with in vitro activity against carbapenem-resistant GNB have just recently been developed. The new molecules include a combination of beta-lactam antibiotics with beta-lactamase inhibitors (BLBLIs), novel beta-lactam antibiotics and drugs that do not belong to the beta-lactam class. Novel BLBLIs include avibactam, relebactam and vaborbactam that show the ability to inhibit Class A carbapenemases-producing bacteria such as *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-Kp) (Toussaint & Gallagher, 2015). New FDA-approved BLBLIs with activity against carbapenem-resistant Enterobacteriaceae (CRE) include ceftazidime/avibactam and meropenem/vaborbactam.

Among other novel beta-lactam antibiotics, ceftolozane has been approved in combination with tazobactam and showed high efficacy against MDR *P. aeruginosa* (Munita et al., 2017). Other non-beta-lactam antibiotics recently approved by the FDA include plazomicin, a novel aminoglycoside and eravacycline (Rodríguez-Avial et al., 2015; Bassetti & Righi, 2014a).

Novel compounds such as cefiderocol (S-649266), a novel siderophore cephalosporin and the association of aztreonam with avibactam are currently under investigation and may provide new tools against other carbapenemases (Falagas et al., 2017; Davido et al. 2017).

The new molecules show promising results when compared to a combination of old molecules such as carbapenems, colistin, tigecycline and aminoglycosides (Shields et al., 2016; Van Duin et al., 2018; Shields et al., 2017; Ayaz et al. 2018). Here, we discuss the characteristics and efficacy of newly FDA-approved compounds with activity against carbapenem-resistant GNB.

Ceftazidime/avibactam has shown activity against CRE and carbapenem-resistant *P. aeruginosa* (Chen et al. 2017). Avibactam is a non-beta-lactam, beta-lactamase inhibitor that inhibits the activity of Ambler Class A (ESBL and KPC), Class C (AmpC) and some Class D (OXA-48) enzymes, but it is not active against metallo-beta-lactamases such as NDM, VIM and IMP (Keepers et al., 2015). Based on the results of Phase 3 trials, ceftazidime/avibactam is approved for use in complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI) and hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

The emergence of resistance has been reported during treatment with ceftazidime/avibactam (Shields et al., 2016), and its use has later been reported in association with other antimicrobials

(Van Duin et al., 2018; Shields et al., 2017; Royo-Cebrecos et al. 2017). Promising results were shown by real-world studies comparing ceftazidime/avibactam with a combination of older antibiotics, such as a carbapenem plus an aminoglycoside or colistin, in the treatment of KPC-producing strains (Shields et al., 2017). Compared to colistin, ceftazidime/avibactam showed lower 30-day adjusted all-cause hospital mortality (9% vs. 32%, respectively, p = 0.001) (Van Duin et al., 2018). In Phase 3 clinical trials, adverse events were similar between ceftazidime/avibactam and comparators, and no safety concerns have emerged for ceftazidime/avibactam from recent studies (Mazuski et al., 2016; Gyarmati et al. 2016; Torres et al., 2017).

Among haematological patients, the experience with ceftazidime/avibactam remains limited. A study including 30 patients showed similar mortality but a higher 14-day clinical cure for those treated with ceftazidime/avibactam (n = 8) compared with other treatments (85.7% vs. 34.8%, respectively, p = 0.031) (Castón et al., 2017).

This novel antibiotic may be an effective alternative for treating haematological patients with CRE, although more data are needed to confirm its efficacy in this patient population.

Meropenem/vaborbactam is a novel Class A and Class C BLBLI and displays a high affinity for serine beta-lactamases (Hackel et al., 2017). In a study including 991 isolates of KPC-producing Enterobacteriaceae, vaborbactam was able to reduce meropenem MIC50 and MIC90 from 32 to 0.06 μg/mL and 1 μg/mL, respectively (Hackel et al., 2017; Sun et al., 2017). Overall, meropenem/vaborbactam has demonstrated high in vitro activity against KPC-producing Enterobacteriaceae (Hackel et al., 2017) but has no activity on Class D and Class B carbapenemases and against CR non-fermenting GNB (Lomovskaya et al., 2017). Meropenem/vaborbactam received FDA approval in August 2017 for the treatment of cUTI based on the results of the TANGO1 trial, showing its superiority versus piperacillin/tazobactam in the treatment of cUTI and acute pyelonephritis (Kaye et al., 2018). Meropenem/vaborbactam was well tolerated with headache, diarrhoea and infusion site phlebitis being the most frequently reported adverse events (Kaye et al., 2018).

In a Phase 3 trial encompassing 72 patients with BSI, cUTI, HAP/VAP, or cIAI due to carbapenem-resistant Enterobacteriaceae, meropenem/vaborbactam was associated with increased clinical cure and lower all-cause mortality. The comparator was best available therapy including ceftazidime/avibactam monotherapy or combination treatment with a carbapenem or an aminoglycoside, polymyxin B/colistin or tigecycline (27% vs. 68%, p = 0.008 and 5% vs. 33%, p = 0.03, respectively) (Ayaz et al. 2018).

Although data in immunocompromised patients are lacking, meropenem/vaborbactam may represent a promising option for the treatment of CRE infections in various patient populations.

Ceftolozane/tazobactam is a BLBLI combination characterised by high activity against *P. aeruginosa*, including strains with resistance caused by derepressed AmpC or upregulated efflux pumps (Livermore et al., 2009), but excluding carbapenemases such as KPC and MBL-producing strains (Takeda et al., 2007). The combination with tazobactam enhances the activity against ESBL-producing Enterobacteriaceae (Armstrong et al., 2015). Ceftolozane/tazobactam is currently approved for the treatment of cIAI, in combination with metronidazole, and for cUTI based on the results of clinical trials (Huntington et al., 2016; Solomkin et al., 2015). Post-marketing studies have explored the efficacy of ceftolozane/tazobactam for the treatment of MDR *P. aeruginosa*, including respiratory infections (Munita et al., 2017; Marschal 2017).

A multicentre, retrospective study including 35 patients with infections due to carbapenem-resistant *P. aeruginosa* treated with ceftolozane/tazobactam showed successful outcome in 74% of the patients (Munita et al., 2017). Another recent study encompassing 101 patients (78% with carbapenem-resistant *P. aeruginosa*) showed overall clinical success rates of 83.2% (Bassetti et al., 2018).

Preliminary studies have shown the efficacy and favourable profiles of ceftolozane/tazobac-

tam among patients with haematological malignancies (Fernández-Cruz et al., 2018; de Souza et al. 2018). In a single-centre study including 19 patients (>60% neutropenic), similar cure rates at day 14 of treatment and lower 30-day mortality were reported among patients treated with ceftolozane/tazobactam compared with those receiving alternative therapies for MDR *P. aeruginosa* infections (Fernández-Cruz et al., 2018).

This compound appears promising due to the increased rates of MDR *P. aeruginosa* among neutropenic patients, including areas where resistances to broad-spectrum antibiotics are relatively low (Righi et al., 2017).

Plazomicin is a novel aminoglycoside characterised by higher activity against KPC-producing bacteria compared to other aminoglycosides (Galani et al., 2012). Plazomicin demonstrated in vitro activity against aminoglycoside-resistant Enterobacteriaceae, ESBL-producing bacteria and CRE (Walkty et al., 2014). A study including 17 patients with BSI or HAP/VAP due to CRE showed lower mortality among those treated with plazomicin compared to colistin, when the antimicrobials were used in combination with meropenem or tigecycline, while creatinine levels were higher among patients treated with colistin compared to plazomicin (38% vs. 8%, respectively) (McKinnell et al., 2017). Plazomicin has recently been approved for the treatment of cUTI. A recent FDA briefing document, however, did not note substantial evidence for recommending plazomicin use in BSI (FDA Briefing Document 2018).

Eravacycline is a novel fluorocycline similar to tigecycline with efficacy against MDR Enterobacteriaceae including ESBL, KPC and OXA-producing strains and *A. baumannii* (Zhanel et al. 2018). Eravacycline has recently received FDA approval for the treatment of cIAI based on the results of a randomised, double-blind, multicentre study showing intravenous eravacycline non-inferiority compared to ertapenem (Solomkin et al. 2017).

In conclusion, novel FDA-approved compounds appear promising for the treatment of MDR GNB. More data, however, are awaited to confirm the superiority of novel strategies in the treatment of MDR GNB and the benefits for haematological patients in real-world practice.

12.5 Prevention Strategies: Antimicrobial stewardship, Infection Control Strategies and Targeted Decolonisation

Haematological patients may show prolonged intestinal colonisation with MDR GNB that poses them at high risk of developing resistant infections, especially during periods of chemotherapy-induced neutropenia and following HSCT (Birgand et al. 2013; Girmenia et al. 2015a; Zuckerman et al. 2011). A survey including tertiary hospitals showed the highest KPC-Kp colonisation rates and KPC-Kp attributable mortality in haematology compared to ICU, internal medicine and surgery wards (Bartoletti et al. 2013). Rates of infections among carriers in haematology, transplant surgery, ICU and medicine were 38.9%, 18.8%, 18.5% and 16%, respectively (Giannella et al. 2014).

In patients undergoing HSCT in areas with significant MDR GNB spread, monitoring of resistant bacteria such as KPC-Kp colonisation is suggested to implement infection control and to potentially guide empirical therapy in neutropenic febrile patients (Girmenia et al. 2015b).

Various studies have analysed the impact of decolonisation strategies in haematological patients but show variable results (Zuckerman et al. 2011; Tascini et al. 2014; Saidel-Odes et al. 2012; Lübbert et al. 2013; Oren et al. 2013; Lambelet et al. 2017). Oral gentamicin and oral colistin used in patients with CRE colonisation accomplish decontamination rates ranging from 37% to 71% (Zuckerman et al. 2011; Tascini et al. 2014; Saidel-Odes et al. 2012; Lübbert et al. 2013; Oren et al. 2013; Lambelet et al. 2017), but the persistence of resistant strains in up to 40% of patients.

Tascini et al. performed a prospective study encompassing 50 consecutive patients with gut colonisation due to gentamicin-susceptible KPC-Kp who received oral gentamicin and 6 months of post-treatment follow-up (Tascini

et al. 2014). Less effective decolonisation occurred among patients with ongoing infections receiving antimicrobial treatment (44% vs. 96%, P < 0.001). Although a lower number of KPC-Kp infections was detected among patients receiving oral gentamicin compared to those who did not (15% vs. 73%, P < 0.001), mortality rates were similar among groups, and 25% persistent carriers presented gentamicin-resistant KPC-Kp colonisation after treatment.

A multidisciplinary consensus statement suggests to consider decontamination in carriers undergoing HSCT (Girmenia et al. 2015b) but highlighted that there is poor evidence to support a recommendation due to the limited experience in haematological populations and the need for further data regarding the risk of resistance selection. Specifically, the selection of colistin resistance could be detrimental since this compound is still often used as a backbone for the treatment of CRE infections (Bassetti and Righi 2014b). Furthermore, the timing to define definitive decolonisation is difficult to establish. A recent randomised trial showed a transient effect of oral colistin administration (2 MU q6h) on MDR/XDR GNB intestinal colonisation (in the 47% of cases due to *K. pneumoniae*) in 62 patients with haematological malignancies (Stoma et al. 2018). Efficacy of colistin treatment was demonstrated among patients receiving colistin versus no treatment (61.3% vs. 32.3%, respectively; p = 0.02) after 14 days, while no statistical difference was seen on day 21 post-treatment among both groups. Lower BSIs were reported in the decolonisation arm in the first 30 days after the intervention (3.2% vs. 12.9%), but the results were not confirmed at the 90-day follow-up. In conclusion, there is currently not enough evidence to recommend a decolonisation with oral antibiotics among haematological patients who are CRE carriers, and the decision should be taken on an individual patient basis.

Haematological patients are particularly exposed to antibiotics for the prevention or treatment of infection due to the frequent episodes of neutropenia caused by multiple courses of immunosuppressive treatments. Collateral damage from the use of broad-spectrum antibiotics (e.g. cephalosporins or quinolones) includes the selection of multiple resistances to different antibiotic classes as well as an increased risk of developing candidemia and *Clostridioides difficile* infection (Das et al. 2011; Gifford and Kirkland 2006). A recent critical appraisal of the European Conference on Infections in Leukaemia (ECIL) guidelines for patients with prolonged neutropenia systematically revised the evidence of FQ prophylaxis impact on BSIs, showing a decreased incidence of BSIs but no impact on overall mortality rates (Mikulska et al. 2018b). Due to FQ toxicity and resistance, it is suggested to weigh the benefits of their use as prophylaxis in patients with severe neutropenia according to the changes in local ecology (Mikulska et al. 2018b).

Due to the frequent exposure to prolonged broad-spectrum antibiotics, haematological patients would largely benefit from antimicrobial stewardship (AMS) programmes which have the objective to limit, when possible, the unnecessary use of antibiotics (Gyssens et al. 2013). AMS programmes in haematology aim to improve outcomes, guarantee cost-effective therapy and reduce adverse effects of antimicrobial use, including collateral damage such as antimicrobial resistance. Elements of therapy optimisation include de-escalation of broad empirical regimens, once the susceptibility test is available, and dose optimisation, especially in severe infections and among critically ill patients (Kaki et al. 2011). Specifically, antibiotic regimens should be individualised according to pharmacokinetic/pharmacodynamic (PK/PD) principles, considering that, similarly to ICU patients, high-risk haematological patients often have large volumes of distribution and may require higher doses and/or extended infusion of antimicrobials (e.g. beta-lactams) to obtain target concentrations (Abbott and Roberts 2012; Lortholary et al. 2008).

Infection control measures are strictly correlated with AMS programmes and share the objective of limiting the number of infections caused by MDR bacteria. Infection control measures in haematology are well established and include patient's isolation and cohorting, strict hand hygiene measures enforcing antisepsis with

alcohol-based hand-rubs, standard barrier precautions, use of single rooms and high-efficiency particulate air (HEPA) filtration for HSCT recipients (Freifeld et al. 2011; Pittet et al. 2000).

To ensure the optimisation of the different aspects involved in AMS programmes, a multidisciplinary approach is necessary, involving microbiologists, hospital pharmacy, haematologists and infectious diseases specialists. Shared protocols, mutual training, frequent clinical rounds with discussion of patient management, antimicrobial drug use and infection control are recommended to ensure a successful collaboration among different specialists. Gyssens et al. have recently summarised the principles of AMS for haematological cancer patients (Gyssens et al. 2013), emphasising the importance of regular reviews of local surveillance data, including rates of antibiotic consumption and resistance, to increase the optimisation of empirical therapy and to develop local protocols and algorithms. The performance of surveillance cultures to document colonisation with MDR pathogens is also important, although their relevance should be supported by data documenting the outcome of patients with BSI caused by different pathogens that may be detected as colonisers. Furthermore, the development of local management algorithms should take into consideration patients' risk stratification (e.g. Multinational Association for Supportive Care in Cancer—MASSC risk index score) as well as the individualised risk assessment for infections due to MDR pathogens. A prompt availability of microbiological results should be guaranteed, and implementation of rapid techniques for identification of susceptibility profiles should be favoured to optimise treatment. When possible, de-escalation or treatment discontinuation should be considered. Tailored de-escalation and discontinuation have proven to be safe in selected high-risk haematological patients (Slobbe et al. 2009; Cornelissen et al. 1995; la Martire et al. 2018), also during pre-engraftment neutropenia (Gustinetti et al. 2018). AMS main interventions and expected benefits are summarised in Table 12.3.

In conclusion, the optimisation of AMS programmes in haematology is crucial in the era of growing microbial resistance. AMS implementation is justified by the global resistance crisis, the limited number of novel antibiotics available against MDR GNB, and high rates of mortality caused by infections due to resistant pathogens in

Table 12.3 Aims and related interventions associated to potential AMS programmes in haematology

Aims	Interventions
• Optimisation of therapy duration. • Reduction of antibiotic resistances.	• Interactive bedside education on antimicrobial drug use. • Reporting of positive clinical cultures. • Implementation of rapid techniques for bacterial identification. • De-escalation to narrow-spectrum antibiotics. • Discontinuation of therapy in stable patients. • Limitation of prophylaxis to selected high-risk patients. • Reassessment of empirical therapy after 48–72 h of treatment.
• Optimisation of antimicrobial dosing. • Reduction of antimicrobial toxicity.	• Use of high doses, beta-lactam extended infusion. • Therapeutic drug monitoring. • Risk stratification for type of infection and disease severity.
• Optimisation of management protocols. • Optimisation of empirical therapy.	• Multidisciplinary approach, protocol sharing. • Performance of surveillance cultures. • Monitoring of BSI outcomes. • Periodic update of local epidemiology data (at least twice yearly). • Surveillance of most common GNB resistance. • Monitor antimicrobial consumption (DDDs). • Perform patients' risk factor analysis for resistant infections.

BSI, bloodstream infections; *GNB*, gram-negative bacteria; *DDDs*, defined daily doses

haematological patients. Infection control measures are paramount and complementary to AMS programmes to prevent the spread of resistant pathogens.

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