Clinical Use of Colistin in Biofilm-Associated Infections

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Jaime Lora-Tamayo, Oscar Murillo, and Javier Ariza

Abstract

Biofilm is an adaptive bacterial strategy whereby microorganisms become encased in a complex glycoproteic matrix. The low concentration of oxygen and nutrients in this environment leads to heterogeneous phenotypic changes in the bacteria, with antimicrobial tolerance being of paramount importance. As with other antibiotics, the activity of colistin is impaired by biofilm-embedded bacteria. Therefore, the recommendation for administering high doses in combination with a second drug, indicated for planktonic infections, remains valid in this setting. Notably, colistin has activity against metabolically inactive biofilm-embedded cells located in the inner layers of the biofilm structure. This is opposite and complementary to the activity of other antimicrobials that are able to kill metabolically active cells in the outer layers of the biofilm. Several experimental models have shown a higher activity of colistin when used in combination with other agents, and have reported that this can avoid the emergence of colistin-resistant subpopulations. Most experience of colistin in biofilm-associated infections comes from patients with cystic fibrosis, where the use of nebulized colistin allows high concentrations to reach the site of the infection. However, limited clinical experience is available in other scenarios, such as osteoarticular infections or device-related central nervous system infections caused by multi-drug resistant microorganisms. In the latter scenario, the use of intraventricular or intrathecal colistin also permits high local concentrations and good clinical results. Overall, the efficacy of intravenous colistin seems to be poor, but its association with a second antimicrobial significantly increases the response rate. Given its activity against inner bioflm-embedded cells, its possible role in combination with other antibiotics, beyond last-line therapy situations, should be further explored.

Keywords

Polymyxin · Biofilm · Cystic fibrosis · Prosthetic joint infection · Implant-associated infection

J. Lora-Tamayo (✉)
Department of Internal Medicine, Hospital Universitario 12 de Octubre, Madrid, Spain
e-mail: jaime@lora-tamayo.es

O. Murillo · J. Ariza
Department of Infectious Diseases, Hospital Universitario de Bellvitge, Barcelona, Spain

The presence of bacterial biofilms in nature, industry, and pathological processes in the human body has attracted increasing interest in recent

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years [1, 2]. The biofilm crucially conditions the bacterial susceptibility to disinfecting substances and antimicrobial molecules, including polymyxins, and has led to a paradigm change in particular clinical scenarios [1, 3, 4]. In the current setting of increasing antimicrobial resistance [5], polymyxins are a last-line therapy, also for biofilm-associated infections. In this chapter, we review the most important features of the biofilm structure, and focus on the activity of polymyxins against biofilm-embedded bacteria. Furthermore, we will analyze the use of high doses and combination therapy in the management of biofilm-associated infections, before outlining the different clinical applications of polymyxins in this scenario.

13.1 The Biofilm Paradigm, The Clinical Problem

The bacterial biofilm is a universal and sophisticated adaptive mechanism of bacterial survival, defined as a structured bacterial population embedded in a self-produced glycoproteic three-dimensional matrix. The formation of a biofilm starts with bacteria attaching to a surface [6], which is typically inert and belongs to a foreign body such as a pacemaker or prosthetic joint, but it may also be the surface of organic tissue such as occurs in the bronchial tree in cystic fibrosis or in sequestrated bone in chronic osteomyelitis [1, 3].

The initial reversible adhesion to the surface is sensed by the bacteria, which induces the expression of several genes that allow a more sustained attachment and the excretion of a polymeric matrix composed of glycoproteins, polysaccharides, and ribonucleic acids [7, 8]. Consequently, cells become encased by a slime-like substance within which the concentration of nutrients and oxygen dramatically reduces. In this particular environment, bacterial cells undergo phenotypic changes and significantly reduce their metabolism: in short, they consume less energy and decrease the rate of replication [1, 9].

Far from being a passive adaptive form, the biofilm structure is a complex and dynamic 3-dimensional matrix. Maturation of the biofilm leads to inner channels being formed that allow media and nutrients to be circulated [6, 10]. When the biofilm achieves a critical size, the outer layers may then detach from the structure, which allows the cells encased within to be released and to recover their planktonic properties. Subsequently, the cells are able to attach to new surfaces and to restart the process. The detachment of the outer layers may occur due to the physical conditions under which the biofilm develops, or may be due to the excretion of digestive enzymes that disrupt the extracellular matrix and release the bacteria [1, 6].

The production of these enzymes is just one example of the bacterial specialization and coordination that occurs throughout the biofilm because of both the local concentration of nutrients and the biochemical system of communication and signaling known as *quorum sensing* [6, 9, 11]. Indeed, when the number of bacteria excreting a particular compound (signal) reaches a critical concentration threshold, new gene expression is triggered in distant cells, which leads to a heterogeneous phenotypic pattern of bacteria within the biofilm and to the presence of specialized subpopulations [7].

In the outer biofilm layers where the concentrations of oxygen and nutrients are higher, bacteria are metabolically more active, whereas the rate of replication is much lower in the deeper layers [3]. Intracellular bacteria may also be found in the biofilm structure [12], as well as specialized surviving forms such as small colony variants [13]. Indeed, the existence of bacteria at various metabolic stages, with specific abilities and phenotypes, is believed to increase the chances of survival when faced with a particular threat.

Importantly, biofilms are known to be tolerant to antimicrobials, and so can survive when exposed to biocidal substances or antibiotics at clinically achievable concentrations. The reasons for this are beyond the classical mechanisms of resistance and can be summarized as follows [1, 3, 4, 14]:

(i) Impaired diffusion of molecules in the biofilm. While most antibiotics are able to diffuse within the glycoproteic matrix, the transition of some may be impaired in the case of voluminous or polymeric molecules [1]. In addition, the presence of extracellular hydrolytic enzymes may inactivate the antibiotic before it reaches bacterial cells [4, 15], or the antibiotic molecule may be held by physical forces, as in the case of positively charged aminoglycosides that are held in the negatively charged biofilm [3, 16].

(ii) Biofilm-embedded bacteria become intrinsically less susceptible to most antibiotics. This is mainly due to the metabolic changes that bacteria undergo when exposed to low nutrient and oxygen concentrations. Antibiotics with activity that is highly dependent on the rate of bacterial growth, for example β-lactams, are particularly affected by the resulting low replication rates of adherent bacteria. This has also been observed in planktonic bacteria which, when exposed to high bacterial density and low nutrient concentrations, enter a phase of stationary growth that makes them tolerant to antimicrobials [3].

(iii) Biofilm-embedded bacteria may express very different phenotypes according to the local environmental conditions and the *quorum sensing*. Thus, they can differentiate to subpopulations that may be particularly resistant to external chemical or physical threats; these constitute the so-called *persisters* [13, 17]. Also, some bacteria found in biofilm-associated infections are known to be intracellular [12]. These phagocytosis-surviving microorganisms may become infection reservoirs because they are less exposed to antibiotics that are unable to either penetrate the eucaryotic cell or reach specific intracellular compartments [18].

(iv) Finally, both the humoral and cellular immune responses have proved to be ineffective for clearing biofilm-associated infections, but instead contribute to the chronic inflammation and damage observed in the surrounding tissues.

Biofilm-embedded bacteria may also express antimicrobial resistance due to conventional mechanisms such as modification of the antibiotic target or cell permeability, the use of efflux-pumps, or the expression of hydrolysing enzymes. Moreover, horizontal gene transmission is increased in biofilms, thus raising the likelihood of resistance developing [4, 19]. In addition, although the rate of cell replication is significantly decreased for biofilm-embedded cells, some bacteria may increase their mutation frequency, especially when it is not normally very high in the planktonic state [20, 21].

13.2 Activity of Colistin in Biofilms

Polymyxin activity on the biofilm of gram-negative microorganisms has been demonstrated in several *in vitro* and *in vivo* models. Most studies have addressed the activity of colistin on biofilms associated with *Pseudomonas aeruginosa* [8, 14, 22–29] because of its prominence in lung infections in patients with cystic fibrosis.

Colistin has a characteristic but different behavior against *P. aeruginosa* biofilms when compared with other antibiotics [8, 14], being dependent on the 3-dimensional structure of the biofilm [30]. As previously discussed, the biofilm contains many different phenotypes of the same bacteria. Indeed, *P. aeruginosa* biofilms grown *in vitro* develop a characteristic 3-dimensional structure that looks like a mushroom. Bacterial cells contained in the outer part of the structure (the cap of the mushroom) are larger, show mobility, and have more active metabolism when compared with cells located in the deeper layers of the inner structure (the stalk of the mushroom) [7, 8]. Other families of antibiotics, such as the aminoglycosides or fluoroquinolones, are able to kill bacteria located in the cap of the mushroom, but are inactive against the less metabolically active bacteria within the stalk [14]. In contrast, various studies have observed that colistin behaves in an opposite manner: it is able to kill the cells within the stalk of the mushroom structure, but has no activity

against the bacterial cells in the outer layers of the cap [7, 8, 14].

As in the case of planktonic bacteria, the mechanism of tolerance to colistin of these metabolically active cells in the outer layers of biofilm is due to modifications in the membrane lipids of the bacterial cells. This depends on the synthesis of 4-amino-4-deoxyarabinoside (4A4D), which binds to the lipid A of the lipopolysaccharide of the membrane and reduces its negative charge. As a result, the affinity of the positively charged colistin is significantly decreased (Fig. 13.1) [8, 26, 31]. Among other regulatory systems, the polymyxin resistance *pmr* operon induces the synthesis of 4A4D in response to various stimuli, including the presence of sub-inhibitory concentrations of colistin or low concentrations of magnesium or calcium [8, 32]. Pamp *et al* demonstrated that the activity of *pmr* was energy-dependent, thus explaining the heterogeneous distribution of colistin tolerance within the biofilm [14].

In addition, the regulatory system PhoPQ influences the synthesis of molecules that modify the electrical charge of the membrane [27, 31, 32]. In *P. aeruginosa*, the activator BrlR induces the expression of several types of efflux pumps such as MexAB-OprM and MexEF-OprN [27]. Chambers and Sauer observed that BrlR downregulates the PhoPQ system in *P. aeruginosa* biofilms and that higher susceptibility to colistin could compensate for the tolerance of those biofilms to quinolone or aminoglycoside antibiotics [27].

Regarding the particular bactericidal activity shown by colistin against less metabolically active cells located in the stalk part of the mushroom, it is important to note that colistin does not

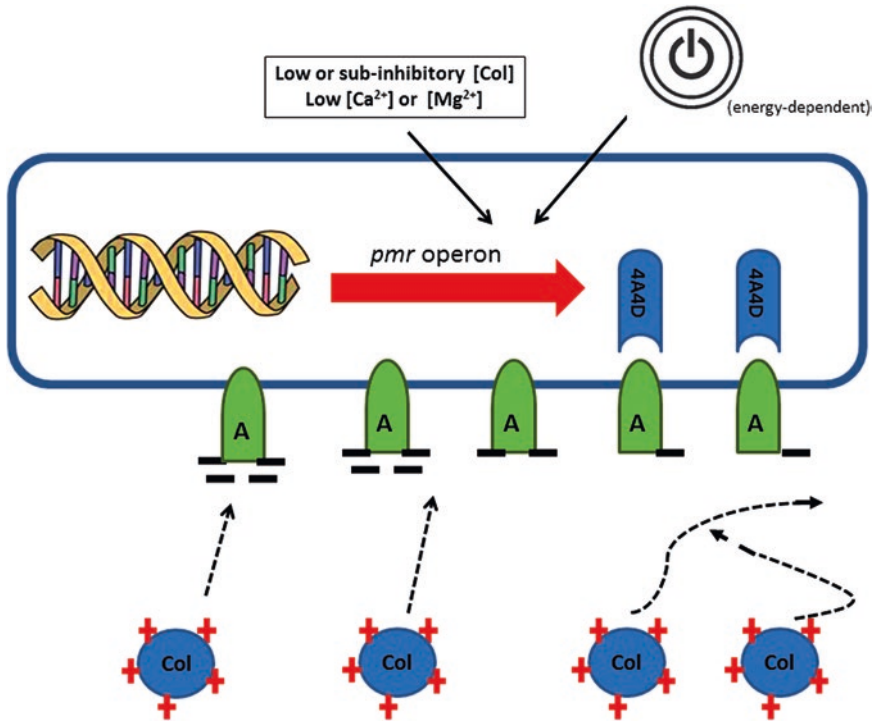

Fig. 13.1 Loss of activity of colistin (Col) in *Pseudomonas aeruginosa* caused by a modification in the net electrical charge of the bacterial outer membrane. This is an energy-dependent mechanism of resistance regulated by the operon pmr. Various stimuli, such as sub-inhibitory concentrations of colistin or low concentrations of magnesium and calcium, may lead to the synthesis of 4-amino-4-deoxyarabinoside (4A4D), which binds to the lipid A of the lipopolysaccharide of the membrane (A), thus reducing its negative charge [7, 14, 27, 31]

seem to be dependent on oxidative stress when targeting *P. aeruginosa*. While the cumulative production of hydroxyl radicals is a common mechanism of killing in metabolically active cells that are exposed to most antibiotic classes, irrespective of their cellular target (e.g., β-lactams, aminoglycosides, fluoroquinolones, and glycopeptides), this is not the case for cationic peptides such as colistin and other substances that modify the membrane permeability. This behaviour may explain the specific activity of colistin against these less metabolically active cells [25].

Several *in vitro* models have shown a decrease in the number of viable biofilm-embedded *P. aeruginosa* cells when exposed to colistin [8, 14, 24, 28, 29]. However, most of these studies have used high concentrations of colistin (10–25 mg/L), which are too optimistic from a clinical perspective, especially in the setting of a biofilm-associated infection. The classic microbiological concepts of minimal inhibitory and bactericidal concentrations (MIC and MBC, respectively) are helpful to predict the activity of antibiotics in planktonic infection, but may not be as useful for biofilm-associated infections [33]. Minimal biofilm inhibitory and eradicative concentrations (MBIC and MBEC, respectively) more accurately reflect the activity of antimicrobials when tested for biofilms [33]. As previously discussed, virtually all antimicrobials are less active against biofilm-embedded bacteria than against their planktonic counterparts [1, 9]. The degree of tolerance against a particular antimicrobial will depend on the specific microorganism and on the maturity and characteristics of the biofilm [2, 22, 34].

To some degree, this is also the case for polymyxins against gram-negative bacilli. In an *in vitro* model of *P. aeruginosa* biofilm, Hengzhuang *et al* showed that colistin had an MBIC of 8 mg/L or 16 mg/L for young or old biofilms, respectively; these required concentrations that were 4–8 times higher than the MIC of 2 mg/L [22]. In this study, the MBEC of a young biofilm was 128 mg/L, which was confirmed by an *in vivo* model of biofilm-associated lung-infection in mice [23]. It is unlikely that intravenous administration of colistimethate sodium (CMS, colistin's prodrug) could provide the required plasma colistin concentrations [35–37].

Therefore, the concerns that exist for achieving sufficiently high colistin concentrations for the treatment of planktonic infections may be extended to biofilm-associated infections. Of course, sub-inhibitory concentrations of colistin may be associated with inadequate therapeutic efficacy [36]. What is more, colistin heteroresistance has been described for several strains of *Acinetobacter* spp. [38], *Klebsiella* spp. [39], and *Pseudomonas aeruginosa* [40]. Selection and amplification of resistant subpopulations after exposure to sub-inhibitory concentrations of colistin is a potential danger that must be considered. Indeed, a recent study using an *in vitro* PK/PD dynamic model of *P. aeruginosa* biofilm found that colistin monotherapy at clinically relevant concentrations initially had no bactericidal activity, which was followed by regrowth and the emergence of colistin-resistance [29].

Based on this PK/PD problem, and supported by experimental models, current recommendations suggest high doses of CMS be administered in combination with a second antimicrobial [37, 41]. The rationale for this is based on the potential for subpopulation synergy: that is, each drug would target the subpopulation that the other drug is not able to kill. In addition, a mechanistic synergy has been proposed based on colistin's mechanism of action [42, 43]. As a cationic peptide, colistin targets the bacterial external membrane and enhances its own uptake, together with that of other molecules, which may favor the penetration of other antibiotics in the bacterial cell [41–43]. With this combination strategy, clinically achievable lower doses of colistin become efficacious and heteroresistant colistin strains might not develop.

In the setting of biofilm infections by gram-negative bacilli, the rationale for colistin in combination with another antibiotic is even greater: as mentioned, colistin is active against the less

active bacteria located in the inner biofilm layers, in contrast with other antibiotics. Therefore, it may have a relevant, distinctive and complementary role in the treatment of biofilm infections caused by gram-negative bacilli. Indeed, the combination of colistin and a second antimicrobial, such as ciprofloxacin or tobramycin, has been shown to be more efficacious than the use of each antibiotic alone, presumably due to the synergistic activity against the whole bacterial population of the biofilm [14, 24].

This may also imply that colistin could be useful not only as a last-line therapy against biofilm-associated multidrug-resistant bacterial infection but also in other settings with poor prognosis, such as prosthetic joint infection caused by fluoroquinolone-resistant gram-negative bacilli [44]. Indeed, in a recent study of foreign-body infection caused by extended-spectrum beta-lactamase-producing *E. coli* in guinea pigs, a higher activity of colistin was demonstrated when combined with gentamycin, fosfomycin, or tigecycline [45].

In the previously mentioned *in vitro* dynamic biofilm model study [29], additivity, synergy, and avoidance of colistin-resistance was observed when colistin was combined with doripenem at clinically relevant concentrations. Interestingly, this was observed not only for carbapenem-susceptible strains of *P. aeruginosa* but also for carbapenem-resistant strains (including two different mechanisms of resistance). Thus, it is suggested that modifications in the bacterial membrane induced by colistin could overcome, at least partially, the mechanisms of resistance to doripenem.

In summary, the rationale for administering high-dose CMS in combination with a second drug remains valid in the setting of biofilm-associated infections in which the overall activity of colistin is typically decreased, as occurs with other antimicrobials. Both *in vitro* and *in vivo* experimental models of biofilm infection support the administration of colistin in combination with other antimicrobials, as each agent targets different sites within the biofilm structure. Finally, there is some evidence to suggest that the modifications in cell permeability caused by colistin may enhance the activity of the second drug against biofilm-embedded bacteria.

13.3 Clinical Experience of Colistin and Biofilm-Associated Infections

Biofilm growth may occur in human infections with or without the presence of foreign bodies. In the former, such as intravascular catheter or pacemaker infections, device removal should be performed whenever possible to improve the cure rate [46]. However, special difficulties exist when seeking to cure those biofilm-related infections that involve non-debrided human tissues or retained medical devices, as can occur in cystic fibrosis and prosthetic joint infection.

The presence of multi-drug resistant (MDR) gram-negative bacilli in the context of a limited therapeutic repertoire of active antimicrobials only adds more complexity to the treatment of biofilm-related infections. Consequently, colistin has mainly been used in the last-line therapy of these difficult-to-treat infections; however, according to the potential benefits of colistin in the setting of bacterial biofilms noted in Sect. 2, this antibiotic might be a suitable alternative to conventional agents against infections caused by other susceptible gram-negative bacilli.

To date, limited clinical experience exists for the use of colistin in the treatment of biofilm-related infections. Apart from aerosolized and intravenous administration, colistin has been administered locally, using the intraventricular route or in cement spacers for central nervous system (CNS) or prosthetic joint infections, respectively. However, neither the optimal dosage of colistin nor the comparative efficacy between colistin alone or in combination have been assessed in this setting. Thus, we review the clinical experience of the use of colistin for the treatment of severe biofilm-related infections in cystic fibrosis and non-cystic fibrosis bronchiectasis, prosthetic joint infection, and CNS device-related infections.

13.3.1 Cystic Fibrosis and Non-cystic Fibrosis Bronchiectasis

13.3.1.1 Cystic Fibrosis

To date, the vast majority of experience with colistin in biofilm-associated scenarios has been accumulated in the context of cystic fibrosis. This congenital disorder produces mutations in the cystic fibrosis transmembrane conductance regulator gene that cause the chloride channel to malfunction. Consequently, the disease affects several human systems, including the lungs, the respiratory airways, the pancreas, and the small intestine, with clinical manifestations dependent on the system affected. In the lungs and respiratory tract, the malfunction produces decreased paraciliary fluid and clearance of microorganisms, which leads to bronchial obstruction, superinfection, inflammation, bronchiectasis, and a loss of respiratory function [47–50].

The life expectancy of patients with cystic fibrosis has improved significantly over recent years, probably because of more aggressive antimicrobial therapy, both in the treatment of infections and as maintenance therapy [48, 51]. Chronic *P. aeruginosa* lung infection is the main cause of morbidity and mortality in cystic fibrosis; indeed, 30% of infants aged 2–5 years and 80% of adults are colonized [52]. Several adaptive mechanisms of *P. aeruginosa* have been related to its ability to survive for long periods in the lungs of patients with cystic fibrosis. Probably the most relevant mechanism is the mucoid-biofilm mode of growth, which allows *P. aeruginosa* to tolerate the immune system, antibiotic therapy, and an anaerobic environment [47].

Colistin is widely used for the treatment of infections by *P. aeruginosa* in patients with cystic fibrosis, both as first line therapy and as a salvage treatment against MDR strains [53, 54]. To date, much of the clinical experience refers to the use of nebulized colistin in intermittently colonized or chronically infected patients [53, 54], with minimal information regarding its intravenous use [55, 56]. However, *in vitro* and experimental studies suggest that both the upper and the lower respiratory airways are infected by *P. aeruginosa*, thus supporting combination therapy with inhaled and intravenous antibiotics, especially in acute exacerbations [47].

The administration of nebulized colistin allows low serum levels and high lung concentrations to be achieved (at least 10 times greater than the MIC value), thus leading to higher efficacy and less drug-related toxicity [57–59]. Furthermore, the conversion of CMS to colistin is higher with nebulized than intravenous administration, probably because there is no renal clearance of CMS in the bronchi, which allows a higher proportion of the prodrug to be hydrolysed to colistin [59]. Thus, compared with intravenous administration, it has been reported that nebulized administration may lead to higher bronchial colistin levels than the MBIC of colistin reported with *P. aeruginosa* biofilm [22, 23]. Currently, a dose of two million IU of CMS every 8–12 h is recommended; although some bronchoconstriction may occur, this dose is usually well tolerated [54, 60]. Recently, significant efforts have been made to improve the aerosolized delivery to achieve superior drug distribution along the airways and to increase medication compliance, as reviewed by Heijerman *et al* [54]. Thanks to modern portable devices, inhalation of colistin as a dry powder is possible over just 2–3 min [61].

In previous studies, the efficacy of aerosolized colistin in combination with oral ciprofloxacin was evaluated and was found to postpone *P. aeruginosa* infection significantly and to maintain pulmonary function [62, 63]. In addition, other studies have revealed similar efficacy between nebulized colistin and tobramycin, especially in decreasing the *P. aeruginosa* sputum density [64, 65]. Of interest, it seems that the emergence of drug-resistant *P. aeruginosa* strains when using aerosolized colistin is less common than occurs when using intravenous colistin for other infections. This is probably related to the higher drug levels achieved with the aerosol route. Furthermore, the emergence of resistance is also less common when colistin is compared with other nebulized drugs [51, 66].

Regarding the intravenous administration of colistin [55, 56, 66], its safety profile and optimal

dosage remain unclear [67]. Previous studies have evaluated the efficacy of colistin, mainly in combination therapy, in the treatment of acute pulmonary exacerbations of cystic fibrosis; in one study, a greater improvement in pulmonary function was reported [56]. Overall, results that are more consistent are needed to evaluate the current role of intravenous colistin for the treatment of pulmonary infections due to gram-negative bacilli in patients with cystic fibrosis. Moreover, the emergence of MDR gram-negative bacilli poses a greater challenge for clinicians, and there is a need to improve our knowledge of the efficacy of colistin in this setting.

13.3.1.2 Non-cystic Fibrosis Bronchiectasis

In comparison with the clinical experience in managing patients with cystic fibrosis, there is much less knowledge of the use of colistin for the treatment of infections in patients with non-cystic fibrosis bronchiectasis. Where research is present, this is limited to the use of inhaled colistin in a limited number of studies. A detailed review of these results is beyond the scope of the present chapter, and we direct readers to a recently published systematic review for further detail [68]. In summary, inhaled colistin has some proven benefits, such as a greater reduction in sputum *P. aeruginosa* load [69]; however, further studies are needed to demonstrate its benefit in the long-term eradication of *P. aeruginosa* or in ameliorating the number of acute pulmonary exacerbations.

13.3.2 Prosthetic Joint and Other Osteoarticular Device-Related Infections

Orthopedic devices (joint prostheses or osteosynthesis hardware) are widely used in current clinical practice to improve the quality of life of patients [70]. However, infection of the devices raises serious concerns, not least because the resulting biofilm-related infections are difficult to treat [46]. The treatment of orthopedic device-related infections must include appropriate and prolonged antibiotic therapy, usually administered at high doses and combined with adequate surgical intervention [70–72].

Depending on the specific type of prosthetic joint infection, management may include debridement and implant retention, replacement with a new prosthesis, or definitive removal of the joint prosthesis [70–72]. However, maintaining the prosthesis poses a major challenge when trying to cure the infection. Concerning infections of osteosynthesis hardware, it seems that internal fixation also shares similarities with prosthetic joint infection. In general, fixation-device related infections are more frequently managed by device removal when compared with prosthetic joint infection.

In this difficult clinical scenario, the most appropriate antibiotic therapy for infections caused by MDR gram-negative bacilli remains a matter of great concern. Again, colistin has been used as a last-line therapy, but its efficacy and the potential benefits of combination therapy with other drugs have yet to be properly evaluated.

Older reports found that the diffusion of colistin into bone was poor [73]; therefore, it was exclusively administered in local beads and cement spacers in the past [74, 75]. This use has progressively been abandoned because there is insufficient knowledge regarding the most appropriate concentration and elution of colistin needed for such cements [76]. While some authorities have discouraged the use of cement spacers in the presence of MDR microorganisms [71], our opinion and that of others argue that the use of colistin-loaded cement spacers might be useful for the treatment of some cases of prosthetic joint infection by MDR gram-negative bacilli [77]. Further studies should explore the potential benefits of administering colistin locally for the treatment of device-related infections.

Clinical experience with intravenous CMS in this field is limited and mainly based on its efficacy as a last-line therapy in difficult-to-treat bone and joint infections caused by MDR gram-negative bacilli [77–80]. Neither the optimal dosage nor the optimal pharmacodynamic parameters of colistin are known for treating these infections.

A recent study was conducted by Valour *et al* with 19 patients suffering from bone and joint infections caused by MDR and extensively-drug resistant (XDR) gram-negative bacilli [78]. In that study, 12 cases were associated with an orthopedic device, and colistin alone was used as salvage therapy in 90% of cases. The authors reported clinical remission in 74% of cases (median follow-up, 28 weeks); however, the outcome of orthopedic-device related infections was clearly worse, leading to a treatment failure of 42%.

Over the last 10 years, we have accumulated data on 22 cases of osteoarticular infection caused by XDR *P. aeruginosa* (Ribera *et al*, communication in the ICAAC, Washington D.C., 2014). In 15 cases (68%), an orthopedic device was involved (8 prosthetic joints). While the combination of colistin and a β-lactam achieved a cure rate of 80%, colistin monotherapy (57% cases) led to poorer results (cure rate, 29%). Of interest, when faced with device-related infections, the combination of colistin with a β-lactam was better when the latter was administered as a continuous infusion (cure rate, 83%) as compared with intermittent boluses (cure rate, 67%).

Overall, colistin seems to offer clinical efficacy against orthopedic device-related infection by MDR or XDR gram-negative bacilli, especially when used in combination with other antimicrobials. In the case of *P. aeruginosa* with full resistance or intermediate susceptibility to β-lactams, the administration of colistin in combination with a β-lactam can improve the outcomes of these infections. Further studies are needed to confirm these results and to explore alternative therapeutic combinations with colistin (i.e., fosfomycin, tigecycline).

Finally, the preclinical and clinical studies that highlight the potential activity of colistin against biofilm-associated infection suggest that the efficacy of colistin needs to be evaluated as a first line therapy in a wider range of orthopedic device-related infections. These include those caused by not only MDR and XDR microorganisms but also less resistant gram-negative bacilli. The poor outcomes associated with prosthetic joint infection by ciprofloxacin-resistant gram-negative bacilli, which is usually treated with β-lactam monotherapy, has been reported [44]. Moreover, the best therapy for the treatment of infections caused by extended-spectrum beta-lactamase or carbapenemase producing *Enterobacteriaceae* needs to be defined.

13.3.3 Central Nervous System Device-Related Infections

Colistin may be the only therapeutic option for CNS infections caused by MDR gram-negative bacilli such as *A. baumannii*, MDR *P. aeruginosa,* or carbapenemase-producing *Klebsiella pneumoniae*. These typically occur in a nosocomial setting in patients with brain damage, as well as those with external ventricular drainage (EVD) or ventriculo-peritoneal shunt (VPS) devices [81]. Patients are usually critically ill, with the infection representing a life-threatening complication that requires optimal antimicrobial therapy. Although the foreign body should be removed to cure the infection [46, 82], the patient frequently needs a replacement CSF diversion to be placed at the same time as the infected material is removed. Therefore, the sterility of the CSF during this procedure is of paramount importance.

In addition to the presence of a foreign-body and bacterial biofilm, the blood-brain barrier (BBB) may significantly impair the diffusion of colistin; thus, excessively low concentrations may occur at the site of infection when the drug is administered intravenously. Experimental and clinical data suggest that only 5% of plasma colistin is able to diffuse into the CNS [83–86]. Diffusion through the BBB does not seem to be affected by efflux pumping by P-glycoproteins, but depends on the permeability of the endothelial tight junctions, which may be increased by inflammatory cytokines [84]. Indeed, the percentage of colistin able to reach the cerebrospinal fluid (CSF) is higher during meningeal inflammation; however, the absolute concentration is usually less than 0.5 mg/L, which is less than that required for most gram-negative bacilli [86, 87].

To achieve higher concentrations of colistin at the infection site, clinicians directly administer CMS into the ventricular or meningeal space [81]. CMS has been observed to convert to colistin in CSF [88] and the available data suggests that repeated doses of intraventricular CMS do not lead to accumulation [84, 85]. In addition to its bactericidal activity, the characteristic anti-endotoxin effect of polymyxins could have a potential favorable effect when treating meningitis. Indeed, the affinity of colistin for the lipopolysaccharide molecule may critically reduce the inflammatory response in the meningeal space [81]. The administration of CMS may be via externalized VPS or EVD ports under extremely sterile conditions: first, 5 mL of CSF must be gently removed to prevent an increase of intracranial pressure; then, the CMS dose is diluted in 3 mL of saline and administered as a bolus over 1–2 min followed by a 2-mL saline flush. Provided the intracranial pressure does not raise too much, the drainage must be closed for at least 60 min to avoid excessive clearance of CMS/colistin [88]. Alternatively, in patients without a VPS or EVD, an Ommaya device or a lumbar drainage may be implanted, although intraventricular administration seems to provide superior diffusion in the CNS than the intrathecal route [81].

Depending on the case, CNS device-related infection may involve the ventricles or the meninges differently. Here, the concomitant administration of intravenous antibiotics with locally administered colistin is desirable, especially when meningitis is present. When MDR gram-negative bacilli are responsible for such infections, intravenous colistin has also been used in some cases [89–92]. While awaiting further studies with greater consistency, some research has found that higher concentrations of colistin are achieved by combined intravenous-intraventricular administration [86], and others have reported the success of this combined approach [90–93]. Given these factors, we consider that the concomitant administration of colistin via the intraventricular route, together with a second intravenous antimicrobial agent, is appropriate for the treatment of severe CNS device-related infection caused by MDR gram-negative bacilli.

Overall, clinical experience with colistin in this setting is mainly based on case reports or small case series, with wide variability in dosing, administration routes (intraventricular versus intrathecal), concomitant intravenous antimicrobials, and the presence or absence of foreign devices. Of note, the greatest experience involves infections caused by *A. baumannii* and, to a lesser degree, *P. aeruginosa*; little information exists regarding other MDR gram-negative bacilli such as the carbapenemase-producing Enterobacteriaceae. Each of these microorganisms may present with different virulence, but it is beyond the scope of this chapter to discuss this in detail. However, regardless of their MDR status, infections by bacteria such as *P. aeruginosa* and *K. pneumoniae* typically cause clinical presentations that are more aggressive, are difficult to treat, and have worse prognoses.

To date, the dose of intrathecal or intraventricular CMS has not been standardized, with doses ranging from 20,000 IU twice daily to 500,000 IU once daily [89, 94–96]. Imberti *et al* studied the pharmacokinetics of colistin in CSF after various doses of intrathecal CMS in 9 patients [88]. Doses of 60,000 IU/d gave C_{max} values of 7–22.1 mg/L and C_{trough} values ≥2 mg/L. The authors concluded that a dose of 125,000 IU/d, as recommended in the Infectious Diseases Society of America guidelines, was probably appropriate based on the notable inter-patient variability observed [82, 88]. In a recent review of more than 100 cases of CNS infection by MDR gram-negative bacilli, Bargiacchi *et al* found no differences in the clinical and microbiological cure rates among patients receiving either ≥125,000 IU/d or < 125,000 IU/d [95].

Clinical and microbiological cure with the use of intrathecal or intraventricular colistin is reported to be high [89, 94–96]. Karaiskos *et al* recently performed a literature review of 83 episodes of CNS infection by MDR *A. baumannii* treated with locally administered CMS (either in monotherapy or with other systemic antimicrobials). A foreign body was present in 63% of cases, and the cure rate was 89%. Toxicity was observed

in 11%, which was mainly due to reversible chemical ventriculitis or meningitis, although there were some cases that involved seizures too [94].

The duration of intrathecal or intraventricular treatment is also highly variable, ranging from 2 to 56 days [94–96]. In the report by Karaiskos, the median time needed to sterilize the CSF was 4 days [94], while Bargiacchi reported that treatments shorter than 7 days in their review had a significantly higher failure rate than longer treatments [95].

In summary, in patients with CNS infection by MDR-gram-negative bacilli, intrathecal or intraventricular administration of CMS is recommended at doses of 125,000 IU per day over at least 7 days. While the eventual foreign body (e.g., the EVD or VPS) will probably need to be removed, locally administered colistin appears to be helpful in sterilizing the CSF before implanting new foreign material. Supported by the current knowledge suggesting colistin heteroresistance and the potential for synergistic interactions, it is also recommended to administer colistin in combination with an intravenous antimicrobial.

13.4 Conclusions

Antimicrobial therapy must be optimized in the case of difficult-to-treat biofilm-associated infections. In many cases, colistin represents an effective last-line therapeutic option because of the increasing incidence of MDR microorganisms. Given that the targets of colistin in the biofilm are different and complementary to those of other antimicrobials, it continues to be recommended that high doses of colistin are appropriate in combination with a second antimicrobial in this setting. The local administration of colistin at the infection site, either nebulized for cystic fibrosis or intraventricular for CNS infections, increases local antibiotic concentrations and improves clinical results. Intravenous administration of colistin seems to be less effective although use in combination with a second antimicrobial significantly increases the response rate. The possible role of colistin in combination with other antibiotics, beyond last-line therapy, should be further explored.

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