Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections

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Increasing multidrug resistance in Gram-negative bacteria, in particular *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*, presents a critical problem. Limited therapeutic options have forced infectious disease clinicians and microbiologists to reappraise the clinical application of colistin, a polymyxin antibiotic discovered more than 50 years ago. We summarise recent progress in understanding the complex chemistry, pharmacokinetics, and pharmacodynamics of colistin, the interplay between these three aspects, and their effect on the clinical use of this important antibiotic. Recent clinical findings are reviewed, focusing on evaluation of efficacy, emerging resistance, potential toxicities, and combination therapy. In the battle against rapidly emerging bacterial resistance we can no longer rely entirely on the discovery of new antibiotics; we must also pursue rational approaches to the use of older antibiotics such as colistin.

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Introduction

One of the greatest accomplishments of modern medicine has been the development of antibiotics for the treatment of potentially fatal infections. However, this has inevitably been followed by the acquisition of resistance towards their antimicrobial activity. Unfortunately, the past two decades have seen a marked decline in the discovery and development of novel antibiotics and a remarkable increase in resistance to those currently available.[1] In particular, there is substantial concern worldwide with the mounting prevalence of infections caused by multidrug-resistant Gram-negative bacteria, in particular *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*; for these species, polymyxins are sometimes the only available active antibiotics.[2–8] Since there have been no promising new chemical entities for Gram-negative infections in the drug development pipeline,[1,4,5] clinicians and microbiologists have been forced to reappraise the clinical value of colistin, a relatively old polymyxin antibiotic. In critically ill patients with such infections, colistin (polymyxin E) is increasingly being used as salvage therapy.[2,4,7] Although the novel agent tigecycline has significant activity against multidrug-resistant *A baumannii*,[9] it is not active against *P aeruginosa* due to efflux by MexXY-OprM.[10]

Colistin is a multicomponent polypeptide antibiotic, comprised mainly of colistin A and B, that became available for clinical use in the 1960s, but was replaced in the 1970s by antibiotics considered less toxic.[2,7,11] There are two forms of colistin commercially available: colistin sulfate for oral and topical use, and colistimethate sodium (sodium colistin methanesulphonate, colistin sulfomethate sodium) for parenteral use (figure 1); both can be delivered by inhalation. Although there have been a substantial number of clinical reports on the successful use of colistin[6,12–24] or polymyxin B[25–27] (which differs by only one aminoacid from colistin) against infections caused by multidrug-resistant *P aeruginosa*, *A baumannii*, and *K pneumoniae*, there is a dearth of information on the clinical pharmacokinetics, pharmacodynamics, and toxicodynamics of colistin; such data are essential for

establishing optimal dose regimens.[2] As a specific example, there are no dosing regimens listed in the product information for the drug appropriate for critically ill patients requiring haemodialysis or continuous renal replacement therapy.[28–30] Most knowledge on the pharmacokinetics of colistin was obtained at least two decades ago when non-specific microbiological assays were used to measure the concentrations of "colistin" in biological fluids.[2]

Because it is approximately 50 years since its discovery and introduction into clinical use, colistin was never subjected to the drug development processes required for compliance with contemporary regulatory requirements. As a result, the pharmacokinetic and pharmacodynamic information required to underpin prescribing recommendations in the product information is lacking. This review will focus on the pharmacology of colistin and new clinical findings from the past 10 years that reflect renewed interest in its use. The scarce and heterogeneous data on the use of colistin in the literature prevents the quantitative synthesis of the impact of this treatment. For the mechanisms of activity and resistance, spectrum of activity and anti-endotoxin effect of colistin, please refer to our recent review.[2]

Pharmacology

Chemistry—important differences between chemical entities

Although widely used in the literature, the terms colistin and colistimethate are not interchangeable.[2,31–34] Colistin (usually used as the sulphate salt) is a polycation, whereas colistimethate (used as the sodium salt) is a polyanion at physiological pH (figure 1). Colistimethate is prepared from colistin by reaction of the free γ-amino groups of the five α,γ-diaminobutyric acid residues with formaldehyde followed by sodium bisulphite.[35]

Colistimethate is not stable in vitro[32] or in vivo,[31,33] and is hydrolysed to a series of methanesulphonated derivatives plus colistin. Colistin is more stable than colistimethate in human plasma.[32] The differences in chemistry between colistimethate and colistin also translate into differences
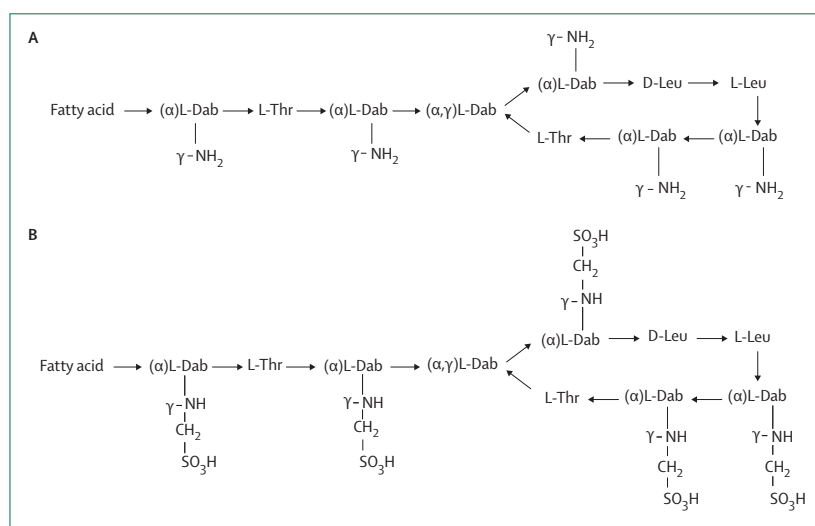
Figure 1: Colistin structures

(A) Structures of colistin A and B; (B) structures of colistimethate A and B. Fatty acid: 6-methyloctanoic acid for colistin A and 6-methylheptanoic acid for colistin B; Thr=threonine; Leu=leucine; Dab=α,γ-diaminobutyric acid. α and γ indicate the respective amino group involved in the peptide linkage.

in pharmacokinetics and pharmacodynamics. Whereas colistimethate is eliminated mainly by the kidney and the urinary excretion involves renal tubular secretion, colistin is eliminated predominantly by the non-renal route because, at least in part, the compound undergoes very extensive renal tubular reabsorption.[33,36] After intravenous administration of colistimethate (sodium), the plasma half-lives of colistimethate are approximately half of those

of the colistin generated from it in vivo in both rats (23·6 [SD 3·9] min *vs* 55·7 [19·3] min)[33] and patients with cystic fibrosis (124 [52] min *vs* 251 [79] min).[31] With respect to antibacterial activity against *P aeruginosa*, recent studies have indicated that colistimethate is a non-active prodrug of colistin.[37] A recent review provides more details on the considerable differences between colistimethate and colistin in their chemistry, pharmacokinetics, and pharmacodynamics.[2] Given these differences, we recommend that the formulations of colistin should be fully described in all future reports, particularly clinical studies, as either colistin sulfate or colistimethate sodium, to avoid any confusion in interpretation of studies with one or both substances.

Inconsistent dose regimens of two major colistimethate (sodium) products

Colistimethate sodium is administered parenterally since it is less toxic than colistin sulfate.[35] The two most common commercially available parenteral formulations of colistimethate sodium are Colomycin (Dumex-Alpharma A/S, Copenhagen, Denmark) and Coly-Mycin M Parenteral (Parkedale Pharmaceuticals, Rochester, USA; table 1). The vials of both formulations contain colistimethate sodium dry powder for reconstitution before administration. Unfortunately, the two products are labelled differently with respect to content. Colomycin is labelled in international units (IU; 500 000 IU, 1 million IU, and 2 million IU per vial);[30] since there are approximately 12 500 units per milligram of colistimethate sodium,[38] there are 40, 80, and 160 mg of colistimethate sodium in each vial size, respectively.[30] The recommended dose for this product for a patient over 60 kg and with normal renal function is 1–2 million IU three times daily, equivalent to 240–480 mg colistimethate sodium per day. By contrast, Coly-Mycin M Parenteral is labelled as containing "150 mg colistin base activity per vial".[28,29] Actually, each vial contains approximately 400 mg colistimethate sodium, which is equivalent to about 5 million IU. The recommended doses for this product are 2·5–5 mg/kg colistin base activity per day in two to four divided doses; which is equivalent to about 6·67–13·3 mg/kg of colistimethate sodium per day.[28,29] Hence, for a patient with normal renal function and bodyweight of 60 kg, the recommended daily dose of Coly-Mycin (400–800 mg) is almost double that of Colomycin (240–480 mg). Unfortunately, despite the fact that this difference has important implications for therapeutic doses, it seems to have been ignored in published works, and brand or product type is often not specified. To further confuse matters, there are several other brands of colistimethate sodium described in some recent clinical reports (Bellon, France;[39] Norma, Greece;[40] Laboratory Bristol-Myers Squibb, Argentina[13]); however, being generic products, it is very difficult to obtain their product information.

Considering that colistin is one of the few and most important antibiotics against multidrug-resistant Gram-

	Colomycin injection	Coly-Mycin M Parenteral
Manufacturer	Dumex-Alpharma A/S, Copenhagen, Denmark	Parkedale Pharmaceuticals, Rochester, MN, USA
Main distributors	Pharmax Limited, Bexley, Kent, UK; Forest Laboratories UK Ltd, Bexley, Kent, UK	Monarch Pharmaceuticals, Inc, Bristol, TN, USA; Link Pharmaceuticals (Australia/ New Zealand), Avalon Beach, NSW, Australia (since July, 2005; Pfizer Australia, before July, 2005)
Labelled content per vial	500 000, 1 000 000 or 2 000 000 IU; about 12 500 units/mg	150 mg colistin base activity
Mass of colistimethate sodium dry powder per vial	40 mg, 80 mg, or 160 mg	About 400 mg
Appearance	Creamy-white powder	White to slightly yellow lyophilised cake
Recommended dose*	≤60 kg bodyweight: 50 000 IU– 75 000 IU/kg per day in three divided doses, equivalent to 4–6 mg/kg per day colistimethate sodium	2·5–5·0 mg/kg per day colistin base activity in two to four doses, equivalent to about 6·67–13·3 mg/kg per day colistimethate sodium
	>60 kg bodyweight: 1–2 million IU three times a day, equivalent to 80–160 mg colistimethate sodium three times per day	
Product-recommended upper limit dose for a 60 kg patient*	480 mg of colistimethate sodium per day	800 mg of colistimethate sodium per day

*For patients with normal renal function.

Table 1: Comparison of the two major types of colistimethate sodium parenteral products

negative bacteria, it is crucial that optimal dose regimens be used to maximise efficacy and minimise the development of resistance.[2] Acceptable safety was demonstrated with 6–9 mg/kg of colistimethate sodium per day (divided into two to three doses) of Colomycin[41–44] and 2·5–5 mg/kg per day colistin base activity with Coly-Mycin,[45] the latter corresponding to an actual daily dose of 6·67–13·3 mg colistimethate sodium per kg per day. The recommended upper daily dose for the two products (480 mg colistimethate sodium per day and 800 mg colistimethate sodium per day for Colomycin and Coly-Mycin, respectively; table 1) differ substantially. Therefore, it is possible that there is potential "under-dosing" when Colomycin is used.

Clearly, with the multiplicity of terms used to express content of vials and dose information, there is major potential to create confusion in the minds of clinicians wishing to administer colistin to patients and in comparing data collected from studies done in various parts of the world. We strongly recommend an international consensus to express the labelled content of parenteral vials and the associated dose information in terms of milligrams of colistimethate sodium. Interpretation of data from pharmacokinetic, pharmacodynamic, and toxicodynamic studies and from clinical trials from various countries would then benefit from a clear definition of the dose of colistimethate sodium administered. The doses presented here have been converted to milligrams of colistimethate sodium.

Minimum inhibitory concentration test: colistin sulfate or colistimethate sodium?

The minimum inhibitory concentration (MIC) is a fundamental element in antibacterial pharmacodynamics and is used widely as a guide in clinical management of patients. Because of the complex chemistry and conversion of colistimethate to colistin, interpretation of an MIC for colistin is dependent upon which entity has been used. In 2000, the US Clinical and Laboratory Standards Institution (CLSI, formerly the National Committee for Clinical Laboratory Standards [NCCLS]) withdrew its guidelines for in-vitro determination of the MIC for colistin against different microorganisms because of its very limited use.[46] In January, 2005, CLSI provided information for testing quality control strains against colistin.[47] The rapid increase in the use of colistimethate sodium necessitates that the measurement of MICs be standardised. Given current knowledge on the chemistry, pharmacodynamics, and pharmacokinetics of colistin and colistimethate,[31–34,36] colistin sulfate, and not colistimethate sodium, should be used for susceptibility testing, for the following reasons. First, colistimethate is a non-active prodrug of colistin against *P aeruginosa.*[37] Second, different brands might have a different content of colistimethate.[33] Third, when determining MICs in broth during overnight incubation at 35°C, hydrolysis of colistimethate to colistin occurs via a complex series of partly methanesulphonated

intermediates. Hence, contamination of colistimethate (sodium) with colistin will generate data from MIC tests and killing experiments that are difficult to interpret. Further, the killing characteristics of this complex chemical mixture, which changes over time during incubation, are likely to be even more complicated. Therefore, MICs obtained with colistimethate (sodium) are only apparent values and could be subject to considerable intralaboratory and interlaboratory variation; subsequently, such MIC estimates are of little or no value.

The currently available breakpoints for colistin susceptibility are based on colistin sulfate. However, at least two different interpretive criteria exist, one from the Société Française de Microbiologie and CLSI (with ≤2 mg/L as the susceptibility breakpoint and >2 mg/L as the resistance breakpoint); the other set by the British Society for Antimicrobial Chemotherapy (BSAC; ≤4 mg/L as susceptible and ≥8 mg/L as resistant).[2] Because of limited pharmacokinetic and pharmacodynamic data, it is still unclear as to which breakpoint is most appropriate.

Pharmacokinetics

The typical serum and urine concentration versus time profiles of colistin after parenteral administration shown in the product information[28,29] are misleading due to the non-specificity of microbiological assays. Such assays are incapable of differentiating the colistin present in the biological sample at the time of collection from the colistin formed in vitro by hydrolysis of colistimethate during the microbiological assay. Very few informative pharmacokinetic studies have been done after an intravenous dose of colistimethate (sodium), most likely because of earlier difficulties with accurate measurement of colistin and colistimethate separately in biological samples.[2]

More recently, two novel HPLC assays have been developed for measuring the concentrations of colistimethate[48] and of colistin[49] in biological fluids, and applied for the first time to pharmacokinetic studies of the two substances.[31,33,36,50] From these and other studies[45,51,52] the overall disposition of colistimethate and colistin can
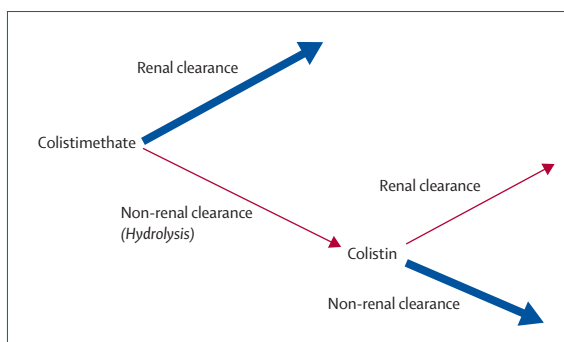

Figure 2: **Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium**

be summarised (figure 2). Colistimethate is predominantly cleared by the renal route but a fraction of the administered dose is converted in vivo to colistin.[33] The colistin formed is mainly cleared by non-renal mechanisms that are as yet not fully characterised. In renal impairment, the elimination of colistimethate by the kidney would be decreased and a greater fraction of the administered dose of colistimethate would be converted to colistin; this explains the need to decrease the dose of colistimethate (sodium) in renally impaired patients who are not receiving renal replacement therapy.[28–30]

In a recent pharmacokinetic study in which patients with cystic fibrosis were administered intravenous Coly-Mycin (213–267 mg every 8 h), an HPLC assay was used.[45] However, the HPLC assay for colistin used in that study, in which the sample pretreatment conditions (54°C or 57°C for 2 h) might have caused substantial in vitro hydrolysis of colistimethate to colistin, would have compromised the accuracy of the data.[31–33] As a result, the study did not yield accurate and useful information on the separate dispositions of colistimethate and colistin. The safety and tolerability of colistimethate was acceptable.[45]
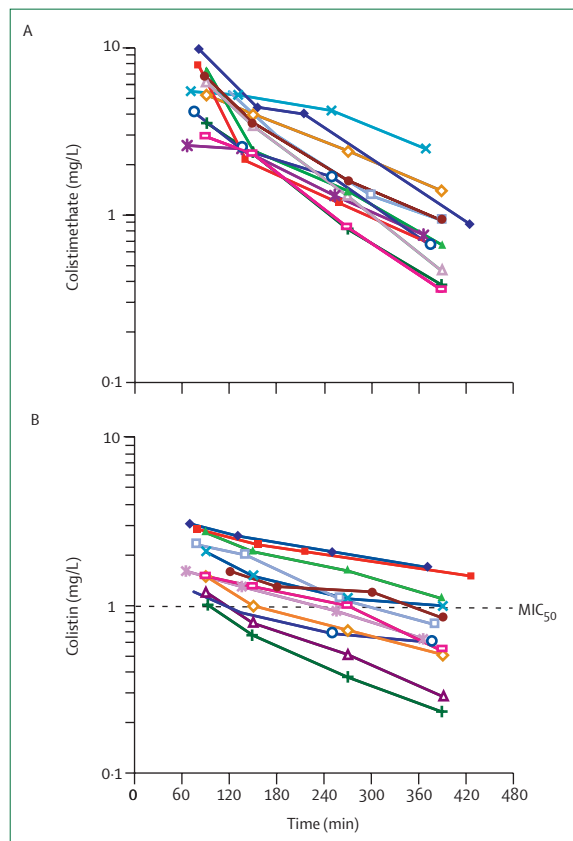
In a pharmacokinetic study in which Colomycin was administered to patients with cystic fibrosis who had normal renal function (figure 3), separate validated HPLC assays for colistimethate[48] and colistin[49] were used. Colistimethate was shown to be converted to colistin in vivo and the ratio of the area under the plasma concentration versus time curve of colistin to that of colistimethate (expressed in molar terms) was 0·69 (SD 0·16).[31] Based on the relative magnitude of the plasma colistin concentrations and reported MIC_{50} of colistin (sulfate) against *P aeruginosa*,[53] it is apparent that the colistimethate (sodium) dosage regimens may have been suboptimal for antibacterial effect in these patients (figure 3B). Plasma concentrations can only be regarded as a surrogate and further investigation on the disposition of colistin in infection sites, such as lung tissues and epithelial lining fluid, are required after intravenous colistimethate sodium. On the basis of the plasma colistin concentrations obtained (figure 3 B) and since the colistimethate (sodium) regimen was well tolerated, dose escalating trials with Colomycin are warranted to maximise efficacy.

Currently, there are no pharmacokinetic data for colistimethate and colistin, generated with reliable analytical (eg, HPLC) methods, in patients with various degrees of renal impairment who are not receiving renal replacement therapy. The product information for both Colomycin[30] and Coly-Mycin[28,29] recommend reduction of the colistimethate dose as renal function declines. Dosage reduction is required because a greater fraction of a colistimethate (sodium) dose will be converted to colistin (figure 2). Clearly, pharmacokinetic data generated with modern analytical methods capable of differentiating colistimethate and colistin in biological fluids are required to confirm how appropriate the current recommendations in the product information are.

In critically ill patients receiving renal replacement therapy, very limited information on the pharmacokinetics of colistimethate and colistin is available and the product information[28–30] for colistimethate sodium injection is not helpful in relation to the selection of appropriate dosage regimens. The product information available in Australia has no data on whether colistimethate is cleared by dialysis,[28] whereas the product information available in the USA states that it is not known if colistimethate is cleared by dialysis,[29] but both suggest that one must maintain the size of each dose while extending the dosage interval. A recent review of antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy[54] recommended a dose regimen of 2·5 mg/kg of colistin base activity (6·67 mg/kg of colistimethate sodium) every 48 hours;[54] but to our knowledge this was not based on any pharmacokinetic data and a very recent case study casts serious doubt upon this recommendation.[50]

The pharmacokinetics of colistimethate and colistin were investigated in a patient who was on continuous

Figure 3: **Pharmacokinetics of colistimethate and colistin in cystic fibrosis patients**
Concentrations of colistimethate (A) and colistin (B) in plasma from patients with cystic fibrosis at steady state administered doses of colistimethate sodium (Colomycin) ranging from 1·63–3·11 mg/kg every 8 h of Colomycin (n=12).[31] Figure used with permission of Oxford University Press.

venovenous haemodiafiltration.[50] The patient was administered Coly-Mycin (Pfizer Australia) intravenously at a dose of 6·6 mg colistimethate sodium per kg of ideal bodyweight every 48 h (corresponding to 2·46 mg colistin base activity per kg every 48 h), as recommended by the product information. The resultant plasma and dialysate concentrations of colistimethate and colistin across a dosage interval are shown in figure 4. The study showed that both colistimethate (7·61% of colistimethate sodium dose) and colistin (2·58% of colistimethate sodium dose) were removed by continuous venovenous haemodiafiltration with similar clearances (colistimethate 11·2 mL/min and colistin 11·9 mL/min). The ratio of the area under the plasma concentration versus time curve of colistin to that of colistimethate sodium (expressed in molar terms) was 0·41. Importantly, during most of the dosing interval (approximately 42 h of 48 h), plasma concentrations of colistin were below the MIC (1 mg/L) for the infecting organism (figure 4); unfortunately, the patient died. The dose regimen used in this patient, which corresponds with the recommendation contained in a recent review,[54] was inappropriate. In this patient, administration at a shorter dose interval (eg, 12 h) would be expected to have generated more favourable plasma concentrations of colistin. Clearly, more definitive dosage recommendations require studies in more patients, and these data are required urgently.

As indicated previously, there is little information on the pharmacokinetics of colistimethate or colistin at infection sites after intravenous administration of colistimethate sodium. Using a microbiological assay, Jimenez-Mejias and colleagues[55,56] reported that the concentration of colistin in cerebrospinal fluid (CSF) was about 25% of that in serum in two patients who received intravenously 5 mg colistimethate sodium per kg per day. Due to the non-specific nature of the microbiological assay, these reports provide no information on the relative concentrations of colistimethate and colistin in serum and CSF.

In a pilot study, very low plasma colistin concentrations (C_{max}<0·064 mg/L) were detected in five patients with cystic fibrosis after nebulisation of 160 mg colistimethate sodium (Rhône-Poulenc Rorer, Amstelveen, Netherlands; product information unavailable).[57] Similarly, low systemic colistin concentrations (C_{max}<0·159 mg/L) were observed in both cystic fibrosis patients (n=5) and healthy volunteers (n=6) after inhaling 25 mg colistin sulfate dry powder.[57] These results have been confirmed in a more recent study.[58]

Pharmacodynamics

Most pharmacodynamic data on colistin are from in-vitro studies.[35,59,60] In-vitro time-kill studies with colistin sulfate or polymyxin B sulfate showed potent, concentration-dependent killing against multidrug-resistant *P aeruginosa*[34,61,62] and *A baumannii*,[63] and a modest post-antibiotic effect only at high concentrations.[34] As discussed
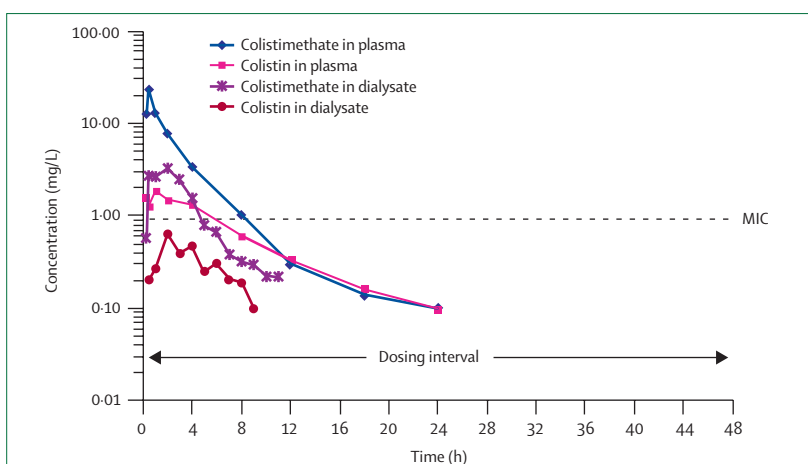

Figure 4: Concentrations of colistimethate and colistin in plasma and effluent dialysate in a patient receiving continuous venovenous haemodiafiltration[50]
Colistimethate sodium was administered at a dose of 6·56 mg/kg of ideal bodyweight every 48 h. Figure used with permission of American Society for Microbiology.

previously, colistimethate is substantially less active than colistin; indeed, colistimethate could be regarded as a non-active prodrug of colistin. One study in an experimental pneumonia model with immunocompetent mice has shown that colistimethate (administered as 10 mg Colomycin/kg every 6 h, supplied by Pharmax) had the weakest antibacterial effect among imipenem (50 mg/kg every 6 h), sulbactam (30 mg/kg every 6 h), tobramycin (15 mg/kg every 6 h), and rifampicin (25 mg/kg every 24 h).[64] In this study, it was not known whether the concentrations of colistin formed from colistimethate were sufficient. A further complication was that the measured concentrations were almost certainly inaccurate because of the hydrolysis of colistimethate to colistin during the microbiological assay. To date, the pharmacodynamic parameters (C_{max}/MIC, AUC/MIC, %T>MIC) for the efficacy of colistin and colistimethate have not been defined in in-vitro pharmacodynamic or in animal models, or indeed in clinical studies. These pharmacodynamic studies are urgently needed to determine the desired pharmacodynamic indicators to devise optimal dosing regimens.

Resistance to colistin

Unfortunately, colistin does not escape development of resistance. There are several suggested mechanisms of resistance to colistin/polymyxin B in Gram-negative bacteria, most of which involve changes in the outer membrane.[65–77]

Interestingly, development of resistance to colistin in multidrug-resistant *P aeruginosa* has not been observed in Denmark[78,79] and the UK,[79,80] despite the use of nebulised colistimethate sodium in combination with oral ciprofloxacin for more than 15 years. By contrast, a very high frequency of mutational resistance to colistin alone was observed in Gram-negative bacteria, including *P aeruginosa*, *A baumannii*, *K pneumoniae*, and

Escherichia coli;[81] and the frequency of mutant selection by polymyxin B in 30 multidrug-resistant, but ciprofloxacin-susceptible, *P aeruginosa* isolates was 10⁻⁷ to 5×10⁻⁹.[82] In a recent study, Gilad and colleagues[83] reported a strong association between the use of colistin and the development of resistance in *A baumannii* clinical isolates collected between 2001 and 2004 in Israel. Of potential clinical concern is the observation of heteroresistance to colistin in 15 out of 16 clinical isolates of colistin-susceptible multidrug-resistant *A baumannii* (most with MICs ≤1 mg/L).[63] Substantial regrowth was observed in static time-kill studies at concentrations above the MIC of colistin (in some isolates even at 32× MIC).[63] It seems that such heteroresistance to colistin is not as common in multidrug-resistant *P aeruginosa* as in multidrug-resistant *A baumannii* (Li et al, unpublished data).

The increasing threat of resistance to colistin highlights the urgent need to define appropriate colistimethate sodium dose regimens for all sub-populations of patients. In addition, it is evident that care is required in the use of colistimethate monotherapy, especially against infections caused by multidrug-resistant *A baumannii*.

New clinical findings

After being almost forgotten for more than 20 years, the recent increase in the use of colistin[7,22,31,41,43,45,55,56,84–86] is a consequence of emerging multidrug-resistant Gram-negative bacteria (particularly in intensive care units), the resultant high mortality rate, and the limited number of therapeutic options available. The prevalence of extended-spectrum beta-lactamase producing organisms, in particular *K pneumoniae*, *E coli*, *A baumannii*, and *Salmonella enterica*, has highlighted the potential of colistin for treatment of such infections.[87–89]

Potential toxicities: re-visited

Nephrotoxicity and neurotoxicity are the most common potential toxicities with parenteral administration of colistimethate sodium.[2,44,84,90–94] However, the toxicity observed in early clinical studies with colistimethate sodium was almost certainly contributed to by a lack of understanding of its pharmacokinetics, pharmacodynamics, and toxicodynamics,[2] and the use of inappropriate doses, possibly caused by confusion in regard to the different nomenclature conventions used for labelling products in different parts of the world.

By contrast with the high incidence of toxicity with intravenous colistimethate (sodium) in early reports,[90–92,95,96] Conway's group[41,42,79,80] and Ledson and colleagues[44] demonstrated satisfactory safety profiles with an intravenous dose of 160 mg every 8 h of Colomycin in patients with cystic fibrosis and normal renal function. Of further interest are recent investigations that have revealed colistimethate to be not as nephrotoxic in patients with cystic fibrosis as previously reported; its nephrotoxicity compared more than favourably with the aminoglycosides, which were originally believed to be less toxic when they replaced colistin 30 years ago.[86,97] One of these studies included 80 stable adult cystic fibrosis outpatients chronically infected with *P aeruginosa* but with no history of preceding renal disease.[86] Creatinine clearance was used as an index of renal function after repeated intravenous administration of aminoglycosides, colistimethate (Colomycin, 160 mg every 8 h in the adult population), and beta-lactams. A correlation between aminoglycoside use and diminishing renal function was observed and colistimethate co-administration potentiated the effect; but colistimethate at recommended doses alone or in combination with non-nephrotoxic antibiotics did not seem to be nephrotoxic.[86] Similarly, colistimethate (Colomycin, 160 mg every 8 h) was less nephrotoxic than tobramycin (10 mg/kg per day) after intravenous administration for 14 days as assessed using a sensitive biological marker, N-acetyl-β-D-glucosaminidase; increased urinary activity of this marker is an early sign of nephrotoxicity.[97] After 98 courses of treatment in 72 patients with cystic fibrosis, median urinary N-acetyl-β-D-glucosaminidase activity increased significantly (p<0·0005) from a value of 0·38 on day 1 to 0·99 and 2·47 on day 14 after treatment with colistimethate (n=56) and tobramycin (n=42), respectively. Even though there were no significant changes in other tests indicative of renal function, the raised activity of N-acetyl-β-D-glucosaminidase on day 14 indicated subclinical renal damage from both colistimethate and tobramycin.[97]

Deterioration in renal function has been observed in some critically ill patients given colistimethate sodium;[39] it is not clear if colistimethate sodium dose had been adjusted appropriately for baseline renal function in some of these patients. More recent studies have reported substantially lower incidence of renal function impairment in critically ill patients.[13,18,22,43,98] Intravenous colistimethate sodium (5·0 mg colistimethate sodium per kg every 24 h in three doses; Alficetin Colistina from the Laboratory Bristol-Myers Squibb Argentina; one vial contains 100 mg colistimethate sodium) was generally well tolerated in critically ill patients with normal renal function in whom it has been used as salvage therapy.[13] Although there is very limited information on the safety of long-term intravenous colistimethate sodium in critically ill patients, Falagas and colleagues[22] investigated the adverse effects from 19 courses of prolonged intravenous colistimethate sodium (Colomycin; mean duration of administration 43·4 [SD 14·6] days, mean daily dose 352 [168] mg, mean cumulative dose 15·2 [7·3] g; dose adjusted for renal function) in 17 patients. The median serum creatinine concentration increased significantly (p<0·001) from baseline by 0·25 mg/dL during the treatment but returned to baseline at the end of treatment (p=0·67). No apnoea or other evidence of neuromuscular blockade was noted in any of these patients.[22]

In another study, Stein and Raoult[99] reported that a dose of 1 million units of colistimethate sodium every 8 h

(information on colistimethate sodium product unavailable) was effective and safe, even when administered over a period of 3–6 months for infections associated with orthopaedic devices caused by multidrug-resistant *P aeruginosa* susceptible to colistin only.[99]

A recent clinical report from the USA described a case of what was considered to be colistin-associated acute renal failure.[100] The dose described was about 8·0 mg colistimethate sodium per kg every 6 h (Coly-Mycin), which suggests that the dose administered was substantially higher than that used in Europe (6–9 mg/kg every 24 h in two to three doses). Plasma concentrations of colistimethate and colistin were not measured. As discussed elsewhere,[101] other clinical factors might also have contributed to the declining renal function.

There is very limited information on the potential neurotoxicity of colistimethate. In a study comparing colistimethate (n=21) with imipenem (n=14) for treating ventilator-associated pneumonia (VAP) due to multidrug-resistant *A baumannii*, no signs of neuromuscular blockade were observed after treatment with intravenous colistimethate sodium (product information unavailable; Bellon, Rhône-Poulenc, Rorer; 2·5–5·0 mg/kg per day divided into three doses for patients with normal renal function);[85] it is unclear whether the dose is in terms of colistimethate sodium or colistin base activity. The authors concluded that intravenous colistimethate seemed to be a safe and effective alternative to imipenem for the management of VAP due to carbapenem-resistant strains of *A baumannii*.[85]

Little information is available on the mechanism of toxicity. Recently Lewis and colleagues[102–104] investigated the effect of polymyxin B and colistin on mammalian urinary bladder epithelium in vitro by electrophysiological methods. Colistin caused an increase in the transepithelial conductance when it was added into mucosal fluid of the rabbit urothelium.[104] At short exposure times (<60 min), the increase in conductance was reversed by either removing colistin from the bath or changing the voltage so that the apical membrane was cell interior positive. At more than 120 min of exposure, the increase was only partly reversible by a change in voltage or removal from the bath, which indicated there is a toxic effect of colistin on the urothelium.[104] Certainly, further investigations on the mechanism(s) of toxicity are required.

It is clear that colistimethate and colistin are potentially nephrotoxic and neurotoxic, and close monitoring is recommended during treatment. It should be noted that when either type of toxicity has been observed, it is usually reversible upon discontinuation of the drug.[29,30,45]

Evaluation of efficacy
Intravenous administration
Greater confidence in the safety of intravenous colistimethate since the 1990s came from reports in patients with cystic fibrosis.[41,42,44,93] Recently, there have been a large number of clinical reports on the efficacy of

intravenous colistimethate in patients with and without cystic fibrosis.[13,17,22,24,39,42,43,55,56,85,86,105,106] It should be noted that the reported studies are not from controlled clinical trials. Table 2 summarises most studies in which intravenous colistimethate was used for infections caused by multidrug-resistant Gram-negative bacteria.

One of the studies in the 1990s that demonstrated promising efficacy and acceptable safety was by Levin and colleagues.[39] These authors used intravenous colistimethate for nosocomial infections caused by *P aeruginosa* and *A baumannii* resistant to aminoglycosides, cephalosporins, quinolones, penicillins, monobactams, and imipenem.[39] Two different colistimethate sodium products were used: Coly-Mycin (6·67–13·3 mg/kg per day in two to three doses) and colistimethate sodium from Bellon, France (product information unavailable). A good outcome occurred for most infections; interestingly, the poorest results were observed in cases of pneumonia (n=20), with only 25% cured.

Since 2005, there have been numerous clinical reports from a group in Greece on the successful treatment of multidrug-resistant Gram-negative bacterial infections with intravenous colistimethate.[6,17,18,22,98,105] Michalopoulos and colleagues[17] reported continuous intravenous infusion of colistimethate (product information unavailable) curing *A baumannii* bacteraemia. The authors indicated that continuous infusion was used to minimise potential toxicity but, unfortunately, did not provide data on patients' renal function. Measuring the concentrations of colistin in plasma and assessing renal function during therapy would have provided valuable information for any relation between the pharmacokinetics and nephrotoxicity of colistin during continuous infusion. More recently, the same research group reported successful treatment of fixation device-related orthopaedic infection by multidrug-resistant *A baumannii* with a bolus intravenous injection of 80 mg colistimethate sodium (Colomycin) followed by 480 mg in a continuous 24-h infusion.[105]

As discussed previously, limited data suggests that colistin gains access to the CSF after intravenous administration of colistimethate. Several case reports have suggested the efficacy of intravenous colistimethate against meningitis caused by multidrug-resistant *A baumannii*.[39,55,56] Katragkou and Roilides reviewed the literature on the successful treatment of central nervous system infections caused by multidrug-resistant *A baumannii* with colistin.[19] Existing experience provides inadequate information to come to any safe conclusions.

Intrathecal/intraventricular administration
Considering the potential nephrotoxicity and neurotoxicity of colistin (sulfate) and colistimethate (sodium) when administered systemically, more direct administration to the infection site might be less problematic. There have been a few recent reports of successful use of intrathecal or intraventricular colistimethate (sodium).[14,20,21,23,24,108,109] Some clinicians have used both intravenous and

Reference	Number of patients	Conditions treated (%)	Pathogens (%)	Colistimethate sodium dose*	Therapy duration (SD)	Outcome
Reina et al[13]	55	Ventilator-associated pneumonia (53%), primary bacteraemia (16%), urinary tract infection (18%), and other infections (13%)	P aeruginosa (35%), A baumannii (65%)	5·0 mg/kg per day (maximum daily dose of 300 mg) divided into three doses; colistimethate sodium from Laboratory Bristol-Myers Squibb (Argentina); product information not available.	13 (5) days	Clinical cure on day 6 of treatment, 15%. Bacteriological cure not assessed
Michalopoulos et al[17]	1	Bacteraemia	A baumannii	160 mg per 24 h by continuous intravenous infusion; product information not available.	14 days	Cured
Michalopoulos et al[18]	43	Various intensive care unit-acquired infections, pneumonia (72%), bacteraemia (33%), sinusitis (2%), urinary tract infection (5%), catheter-related infection (7%), and surgical wound infection (5%)	P aeruginosa (81%), A baumannii (19%)	240 mg every 8 h; Colymycin or colistimethate sodium from Norma (13 333 units/mg; Athens, Greece)	18·6 (5·8) days	Clinical cure of infection observed in 69·8% of patients, clinical improvement in 4·7%, and clinical failure in 25·6%
Falagas et al[22]	17	Pneumonia (68%), bacteraemia (5%), urinary tract infection (11%), meningitis (11%), and surgical site infection (5%)	P aeruginosa (60%), A baumannii (25%), K pneumoniae (10%), Enterobacter cloacae (5%)	Daily dose 352 ± 168 mg Colomycin or colistimethate sodium from Norma (Athens, Greece)	43·4 (14·6) days	Cured 52·6%, improvement 21·1%, unresponsiveness 26·3%
Levin et al[39]	59	Pneumonia (33%), urinary tract infection (20%), primary bloodstream infection (15%), central nervous system infection (8%), peritonitis (7%), catheter-related infection (7%), surgical site infection (7%), and otitis media (2%)	P aeruginosa (35%), A baumannii (65%)	6·67–13·3 mg/kg per day up to a maximum dose of 800 mg; Coly-Mycin or colistimethate sodium from Bellon (Rhône-Poulenec Rorer, France; product information not available.	12·6 (6·8) days	A good outcome occurred for 58% of the patients with 25% in pneumonia, 83% in urinary tract infection, 78% primary bloodstream infection, 80% in central nervous system infection, 50% in peritonitis, 75% in catheter-related infection, 60% in surgical site infection, and in 100% with the patient with otitis media infection
Conway et al[42]	53	Acute respiratory exacerbations in patients with cystic fibrosis	P aeruginosa	160 mg every 8 h, Colomycin	12 days	All patients showed clinical improvement
Markou et al[43]	24	Ventilator-associated pneumonia (62·5%), empyema thoracis (4%), post-traumatic meningitis (4%), sinusitis (4%), urinary tract infection (4%), catheter-related sepsis (12·5%), and sepsis of unknown primary origin (17%)	P aeruginosa (76%), Acinetobacter spp (24%)	3 million units every 8 h, colistimethate sodium from Norma (Athens, Greece)	13·5 days (range 4–24)	Clinical response 73%, survival at 30 days 57·7%
Jimenez-Mejias et al[55]	1	Meningitis	A baumannii	5 mg/kg every day in four doses; product information not available	15 days	Cured
Garnacho-Montero et al[85]	21	Ventilator-associated pneumonia (100%)	A baumannii	2·5–5·0 mg/kg every 8 h, colistimethate sodium from Bellon (Rhône-Poulenec Rorer, France); product information not available.	14·7 (4·1) days	Cured 57%
Linden et al[107]	23	Pneumonia (78%), bacteraemia (35%), wound infections (13%), intra-abdominal infections (26%), endocarditis (4%), and other infection (22%)	P aeruginosa	All patients required dose adjustment for diminished or absent renal function; Coly-Mycin	Median 17 days (range 7–36)	Favourable therapeutic outcome 61%, unfavourable therapeutic outcome 39%, died while receiving therapy 30%, experienced relapse 13%, survived through end of therapy 70%, and through end of hospitalisation 39%
Kasiakou et al[105]	2	Fixation device-related orthopaedic infections	A baumannii	A bolus intravenous injection of 80 mg colistimethate sodium followed by 480 mg in a continuous 24 h infusion (patient 1); 160 mg every 8 h (patient 2); Colomycin	36 and 22 days	Cured
Jimenez-Mejias et al[56]	1	Meningitis	A baumannii	5 mg/kg every day in four doses; product information not available	30 days	Cured
Fulnecky et al[106]	1	Post-surgical meningitis	A baumannii	1·25 mg/kg every 12 h; product information not available	10 days	CSF remained free of A baumannii throughout the rest of the hospitalisation

*Doses were for patients with normal renal function. Administration route was short intravenous infusion (5–30 min) unless specified otherwise. In cases where the product information is not available, it is uncertain whether the dose is in terms of colistimethate sodium or colistin base activity.

Table 2: **Characteristics and outcomes of treatment with intravenous colistimethate sodium for infections caused by multidrug-resistant Gram-negative bacteria in some recent clinical reports**

intrathecal/intraventricular administration of colistimethate (sodium).

Bukhary and colleagues[23] reported a case of nosocomial meningitis caused by multidrug-resistant *A baumannii* in both blood and CSF in a 23-year-old woman. Although intravenous colistimethate (2 million IU every 6 h, product information unavailable) with moxifloxacin (400 mg every 8 h) improved the patient's condition, a positive CSF culture remained. However, 2 days after intraventricular colistimethate (125 000 IU every 12 h in 5 mL normal saline) was given, the CSF culture was negative, and there were no apparent side-effects during the 3 weeks of colistimethate treatment.[23] Kasiakou and colleagues[20] used intraventricular administration of colistimethate (1·6 mg every 24 h, product information unavailable), amikacin (5 mg every 24 h), and teicoplanin (10 mg every 24 h) and intravenous administration of colistimethate (80 mg every 8 h, product information unavailable), amikacin (500 mg every 12 h), and teicoplanin (400 mg every 24 h) to successfully treat a patient who developed five episodes of meningitis, all caused by multidrug-resistant *P aeruginosa* and *A baumannii*, during his 7-month hospitalisation after head trauma. The contribution of colistimethate to the overall outcome is unclear. In another study, two cases of meningitis and ventriculo-peritoneal shunt infections caused by multidrug-resistant *P aeruginosa* were cured with intrathecal colistimethate (Coly-Mycin, 10 mg/day) after development of nephrotoxicity associated with its intravenous administration.[14]

Even though there is still limited knowledge of the value of intrathecal/intraventricular administration of colistimethate, it seems to be a potentially safe and effective option for treating central nervous system infections caused by multidrug-resistant *P aeruginosa* and *A baumannii* when intravenous administration is not practicable or has not been effective.

Inhalation

There is extensive experience with the inhalation of colistimethate sodium and colistin sulfate in patients with cystic fibrosis.[78–80,110–115] Chest tightness and bronchospasm are potential side-effects.[116–118] Colistimethate (sodium) is associated with fewer adverse effects than colistin (sulfate).[111] The dosage for colistimethate sodium is usually 40–60 mg two or three times a day. Inhalation of colistimethate sodium reduced the number of lower respiratory samples containing *P aeruginosa* in patients with cystic fibrosis with early colonisation.[78,115,119]

By contrast with the extensive use of colistimethate sodium inhalation in patients with cystic fibrosis, there is very little experience in patients without this disease—eg, those with nosocomial pulmonary infection caused by multidrug-resistant *A baumannii* or *P aeruginosa*.[24,40,120–122] The safety and effectiveness of aerosolised colistimethate (sodium) as an adjunct to intravenous antimicrobial therapy for the treatment of Gram-negative nosocomial pneumonia has been assessed in eight patients in intensive care, six of whom had VAP.[40] Seven of eight infections were caused by multidrug-resistant *A baumannii*, the other by *P aeruginosa*; four of eight isolates were susceptible only to colistin. The daily dose of aerosolised colistimethate sodium was about 120–480 mg (divided into three or four doses), the mean duration of administration was 10·5 days, and seven of the eight patients received concomitant intravenous treatment with other antimicrobial agents.[40] The pneumonia responded to treatment in seven of the patients (four were cured and three improved). One patient deteriorated and died from septic shock and multiple organ failure. None of the patients experienced chest tightness, bronchoconstriction, or apnoea. Two patients who had a history of chronic obstructive pulmonary disease received concurrent treatment with inhaled β_2 agonist. Only in the patient who died did renal function worsen during aerosolised colistimethate sodium treatment (baseline serum creatinine increased by 1·4 mg/dL). In view of the very low systemic exposure after colistimethate sodium inhalation, it is unlikely that colistin was a major contributor to the renal impairment in this patient, who also had polycystic kidney disease. Thus, aerosolised colistimethate (sodium) could provide beneficial adjunctive treatment in the management of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria.[40]

Combination therapy with colistin

There are a very limited number of studies that have formally evaluated the efficacy of combinations of colistimethate (sodium) or colistin (sulfate) with other antibiotics.

The synergy of colistin with rifampicin has been demonstrated in vitro against multidrug-resistant *A baumannii*.[123–126] Petrosillo and colleagues[127] investigated the clinical outcome in 14 patients with VAP caused by carbapenem-resistant *A baumannii*, *P aeruginosa*, or both, who were treated with intravenous colistimethate sodium (2 million units every 8 h, adjusted for creatinine clearance; product information unavailable) and rifampicin (600 mg every 24 h). The treatment resulted in microbiological clearance of carbapenem-resistant *A baumannii* infection in nine (64%) of the patients, with limited side-effects (one patient had deterioration in renal function). Unfortunately, there was no control group not treated with rifampicin; hence the question of synergy was not directly addressed in this clinical study, only that the combination provided successful therapy.[127]

In the treatment of serious infections in patients without cystic fibrosis, Kasiako and colleagues[98] did a retrospective cohort study to assess the safety and effectiveness of intravenous colistimethate sodium (Colomycin or colistimethate sodium from Norma; doses adjusted on the basis of serum creatinine levels) in combination with other antimicrobial agents (meropenem, ampicillin-sulbactam,

ciprofloxacin, piperacillin-clavulanic acid, imipenem, amikacin, or gentamicin). No major toxicity was observed; however, the efficacy of the combination treatments was difficult to assess because of the limitations of study design.[98]

A combination of nebulised colistimethate sodium (Lundbech, Copenhagen, Denmark; product information unavailable; 2 million units every 8 h) and oral ciprofloxacin (10–20 mg/kg every 12 h) has been used in a Danish cystic fibrosis centre for aggressive eradication therapy of lower respiratory tract infections by multidrug-resistant *P aeruginosa,* and the approach has been adopted more widely.[78] The outcome has been very encouraging: chronic *P aeruginosa* infection was prevented in 85% of patients treated with the combination compared with only 42% in the non-treated group ($p<0.05$).[78] Furthermore, in spite of its use against intermittent *P aeruginosa* colonisation for 15 years by this group, there has been no development of antibiotic resistance.[78]

As indicated above, a limitation of most clinical studies is the lack of control groups without the combination treatment; this limitation is often imposed by practical and ethical considerations. In the context of increasing resistance to colistin, a more systematic examination of the potential for synergy between colistin and other antibiotics is warranted.

Conclusions

Although colistin has been used increasingly for multidrug-resistant Gram-negative bacterial infections due to the alarming resistance to many other currently available antibiotics, its clinical use has been restricted by a dearth of information on its pharmacokinetics, pharmacodynamics, and toxicodynamics. Clearly, infectious disease clinicians and their patients will be in an even more precarious position than currently exists if resistance to colistin becomes widespread. Given that colistin was developed in the 1960s, before contemporary drug development procedures were introduced, there are substantial gaps in the pharmacological knowledge of this old antibiotic. Therefore, it is imperative that clinical pharmacokinetic, pharmacodynamic, and toxicodynamic studies be done. The findings from these studies should be integrated to inform the design of rational dosage regimens for sub-populations of patients so as to maximise the antibacterial activity and minimise the development and prevalence of resistance. In the battle

against rapidly emerging bacterial resistance we can no longer rely entirely on the discovery of new antibiotics; we must also pursue rational approaches to the use of older antibiotics such as colistin.

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Search strategy and selection criteria

Data for this review were obtained from publications identified by systematically searching PubMed with "colistin". We also reviewed data presented at the major antimicrobial chemotherapy meeting, Interscience Conference on Antimicrobial Agents Chemotherapy. Papers on "New clinical findings" focused on those published since 1997.

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