PRODUCT MONOGRAPH for Intravenous Fosfomycin

(fosfomycin disodium)

IV Fosfomycin from InfectoPharm available in many countries:

Please contact us for your local partner/distributor

Registered and available soon under the trade name Fomicyt® in the following countries: Belgium, Czech Republic, Hungary, Slovakia and Romania.

Information as of September 2020

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Introduction

Fosfomycin is the only member of the epoxide class of antibiotics. It is a truly unique antibiotic because of its low molecular weight and its unique mode of action. It exerts a rapid bactericidal effect by inhibiting bacterial cell wall synthesis at an earlier step than β-lactams or glycopeptides. Fosfomycin is effective against infections caused by a variety of gram-positive and gram-negative pathogens, including nosocomial problem bacteria like *Enterobacterales*, *Staphylococcus* spp., *Enterococcus* spp., and *Pseudomonas aeruginosa*. The antimicrobial activity of fosfomycin also extends to strains expressing several mechanisms of reduced sensitivity towards other antibiotics. This includes producers of extended-spectrum β-lactamases or carbapenemases of all Ambler classes (including metallo-β-lactamases), methicillin or glycopeptide resistance as well as multidrug- or extensively drug-resistant strains.

Fosfomycin quickly penetrates into skin and soft tissues, the urinary tract, muscles, bones, heart, lung, the cerebrospinal fluid (CSF), abscesses and bacterial biofilms, among other tissues with poor accessibility, and achieves concentrations well above the minimal inhibitory concentration (MIC) of relevant pathogens. These properties make intravenous fosfomycin a powerful agent for the empiric or targeted combination therapy of difficult-to-treat or complex infections – even biofilm-related infections – when the use of other standard antibiotics must be considered inappropriate. Fosfomycin is suitable for both first- and second-line as well as rescue therapy, depending on the clinical and microbiological situation. Given its advantageous pharmacological profile, fosfomycin is particularly useful for deep-seated infections with or without involvement of foreign devices or implants including intra-abdominal infections, brain abscesses or lung infections, as well as bone infections including spondylodiscitis and diabetic foot infections. Since fosfomycin crosses the blood/brain barrier, it is also an excellent treatment option for CNS infections such as bacterial meningitis or neurosurgical implant-associated infections.

This clinical use is already daily practise in countries with a long-standing and well-established clinical experience with intravenous fosfomycin such as Germany and Austria, where it is very often used for the treatment of patients with methicillin-sensitive *S. aureus* infections. Complicated infections with *S. aureus* with a deep focus still represent a situation not adequately covered by standard therapy.

For most of the licensed indications, fosfomycin is currently used in combination therapy, for example in bone and joint infections, complicated urinary tract infections (cUTI), hospital-acquired pneumonia including ventilator-associated pneumonia (HAP/VAP), bacterial meningitis including brain abscess, infective endocarditis, complicated intra-abdominal infections (cIAI), complicated skin and soft-tissue infections (cSSTI) and bacteraemia/sepsis of unknown origin or occurring in association with or suspected to be associated with any of the infections mentioned above. In monotherapy, fosfomycin should only be considered in complicated urinary tract infections. Cross-resistances with other antibiotics do not occur because of the unique chemical structure of fosfomycin. No cross-allergies with other antibiotics or any clinically relevant interactions with other drugs, stimulants, or foods are known. Moreover, fosfomycin can be combined with a broad spectrum of other antibiotics because of its additive and synergistic activities. Fosfomycin is well tolerated, even at high doses, and is authorised for use in (premature) neonates, infants, children, and elderly patients without any age limitations. Common adverse events include electrolyte disturbances (e. g., hypernatraemia and hypokalaemia), gastrointestinal symptoms, or skin rash

and do not usually call for a discontinuation of treatment. Furthermore, fosfomycin is not nephrotoxic and can be administered to patients with impaired renal function or requiring renal replacement therapy. Study data across many different countries show that susceptibility rates of clinically relevant pathogens towards fosfomycin remain at consistently high levels despite its clinical use for more than 40 years in various countries. This is one of the reasons why intravenous fosfomycin therapy has experienced an international revival in recent years, given the increasing global burden of pathogens resistant to various antibiotics. Problem bacteria such as extended-spectrum β-lactamase (ESBL)-producing enterobacteria, methicillin-sensitive and -resistant *Staphylococcus aureus* (MSSA/MRSA), carbapenemase-producing *Klebsiella pneumoniae*, vancomycin-resistant enterococci (VRE) and multidrug-resistant (MDR) *P. aeruginosa* are only a few examples of the growing list of difficult-to-treat and resistant species. Furthermore, biofilm-associated infections are a challenge in therapy because many standard antibiotics are not effective in these situations. According to recent data, intravenous fosfomycin is a very promising option in this respect as part of various combination regimens. Fosfomycin is included in the WHO list of essential medicines for the treatment of adults and children within the RESERVE group of antibacterial medicines as a treatment option for highly specific patients and settings and when other alternatives would be inadequate or have already failed (e. g., serious life-threatening infections due to multidrug-resistant bacteria). The WHO recommendation allows first- and second-line use of fosfomycin for treatment of patients with difficult-to-treat infections – particularly in serious life-threatening conditions and/or clinical patient settings with limited therapeutic options or in which alternative treatments have limitations such as side effects. In addition to this, intravenous fosfomycin is recommended for various indications in European and national guidelines, e. g., in Austria, France, Germany, Spain, and the UK.

Intravenous fosfomycin is currently licensed in most European countries with a harmonised product information with identical indications and dosages. The product is available in Canada and is awaiting marketing authorisation in the USA. Worldwide, the product is currently registered and available in many additional countries including middle and South America and Asia and is undergoing regulatory approval in further parts of the world.

1 History and development of fosfomycin

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Fosfomycin is a naturally occurring antibiotic that was discovered and isolated in 1969 from various *Streptomyces* strains (*S. fradiae*, *S. viridochromogenes*, *S. wedomorensis*) (Hendlin *et al.* [146]). It underwent clinical development in the 1970s and 1980s and was subsequently introduced into clinical practice in several European countries. The use of fosfomycin increased slowly due to discrepancies between *in vitro* and *in vivo* efficacy. As outlined in Section 2.3 (Mechanism of action), fosfomycin requires glucose-6-phosphate for its transport into the bacterial cytosol so that it can exert its antimicrobial activity. More than a decade passed before *in vitro* testing procedures were standardised, including the addition of glucose-6-phosphate to produce a closer match to the *in vivo* situation (Andrews *et al.* [16]). A recent referral by the European Medicines Agency (EMA) revaluated and harmonised the product information with respect to indications and dosages throughout Europe and reconfirmed the drug's good efficacy and safety profile (EMA [92]); see also Table 1.

The efficacy and safety of fosfomycin have been established in more than 60 clinical trials including randomised controlled trials (RCTs, carried out with more than 2 000 patients).

Table 1: History of the development of intravenous fosfomycin.

Date	Development
1969	Discovery of the active substance fosfomycin in *Streptomyces* spp.
1970	Chemical synthesis of fosfomycin
1972–1973	Phase I clinical trials in Japan
1973–1974	Phase II and III clinical trials in Japan
1974	Elucidation of mechanism of action
1976–1979	Clinical development (Phase II–III) at Boehringer Mannheim, Germany
May 1980	First market authorisation in Germany obtained by Boehringer Mannheim
1983	14 years after its discovery, it was demonstrated that the transport mechanism of fosfomycin into the bacterial cytosol requires glucose-6-phosphate
October 1998	InfectoPharm becomes Marketing Authorisation Holder for Infectofos® in Germany
2014–2017	InfectoPharm obtains Marketing Authorisation in the United Kingdom, Ireland, the Netherlands, Italy, Greece, Poland, Croatia, Sweden, Denmark, Norway and Finland
2019	Marketing Authorisation in Canada
2020	Art. 31 Referral harmonising indications and dosing regimens within the EU
2020 and continuing	Further regulatory submissions in various countries in progress

2 Fosfomycin – product profile

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2.1 Summary

- Fosfomycin is your reliable partner for treating challenging infections.
- Fosfomycin is a broad-spectrum antibiotic active against both gram-positive and gram-negative pathogens.
- Because of its unique mode of action and absence of cross resistances, it is active against
  - staphylococci including MRSA,
  - enterococci including VRE,
  - enterobacteria including ESBL- or carbapenemase-producers including metallo-β-lactamase forming isolates,
  - multidrug-resistant *Pseudomonas aeruginosa*.
- Fosfomycin is the sole member of its class of antibiotics.
- The excellent tissue kinetics and bactericidal activity of this tiniest antibiotic under clinical conditions make fosfomycin the first choice for empirical or pathogen-directed antibiotic treatment of patients with severe and difficult-to-treat infections.
- Fosfomycin is an excellent combination partner due to its additive or synergistic activity when combined with clinically important antibiotic classes.
- Fosfomycin is an option for patients with β-lactam allergy. Due to its unique structure, no cross-allergies are known.
- Fosfomycin has an excellent safety profile without limitations regarding patient age or treatment duration. Fosfomycin does not interact with other substances.
- Fosfomycin appears to be more effective under acidic or anaerobic conditions.

2.2 Chemical characterisation, pharmaceutical form and stability

- Fosfomycin is the sole member of the class of epoxide antibiotics.
- Low molecular weight with high penetration capability, despite its hydrophilic character.

Fosfomycin contains fosfomycin or (1*R*,2*S*)-*cis*-(1,2-epoxypropyl)phosphonic acid ($C_3H_7O_4P$; MW: 138.06 g/mol) as its active substance. Fosfomycin is a small-molecule broad-spectrum antibiotic first isolated from *Streptomyces* species in 1969 (Hendlin *et al.* [146]). Fosfomycin is unique because of its epoxide structure and low molecular weight, being the smallest antibiotic known to date (Figure 1).

Fosfomycin – the tiniest antibiotic in clinical use

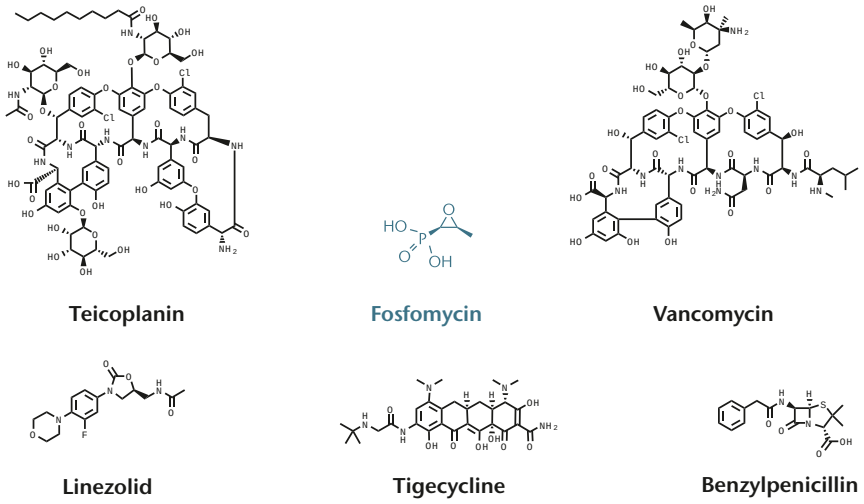


Figure 1: Fosfomycin compared to other antibiotic molecules in clinical use.

For intravenous administration, the highly water-soluble and hydrophilic disodium salt of fosfomycin (fosfomycin disodium, $C_3H_5O_4PNa_2$; MW: 182.03 g/mol) is employed. The pK_a values of the two acidic protons of fosfomycin in water at 25 °C are 6.5 and 5.0, respectively. The pH of the ready-to-use fosfomycin solution is 7.5. Fosfomycin is active over a pH range from 6.0 to 8.0. For the displacement volume and preparation of fosfomycin, please refer to the current Summary of Product Characteristics. Solutions prepared under aseptic conditions are chemically stable in a refrigerator (at 2–8 °C) for at least 24 hours, if protected from light. Fosfomycin should be dissolved exclusively in water for injection or in 5% or 10% glucose solution for infusion. Other diluents, in particular sodium chloride solutions, must not be used. Fosfomycin solutions should not be mixed with other parenteral preparations. However, laboratory data simulating Y-site administration showed that fosfomycin at a concentration of 30 mg/mL was physically compatible with 73/99 (77%) of the i. v. drugs tested, including relevant hospital antibiotics and at common concentrations and solvents (Monogue *et al.* [229]).

Fosfomycin contains succinic acid as an excipient to improve the local tolerance of the drug for veins (Traunmüller *et al.* [330]).

2.3 Mechanism of action

- The unique chemical structure of fosfomycin mimics a natural precursor in bacteria cell wall synthesis.
- Fosfomycin inhibits bacterial cell wall synthesis at an earlier stage than β-lactams.
- Fosfomycin appears to be more effective under acidic or anaerobic conditions.

Fosfomycin exerts its bactericidal effect on proliferating bacteria through a unique mechanism of action that was first described in 1974 (Figure 2): Fosfomycin irreversibly blocks the initial steps of peptidoglycan synthesis initiated by uridine diphosphate-*N*-acetylglucosamine enolpyruvyl transferase (*MurA*) because of its structural similarity with the physiological cofactor phosphoenolpyruvate (PEP) (Kahan *et al.* [164]).

Mechanism of action of fosfomycin

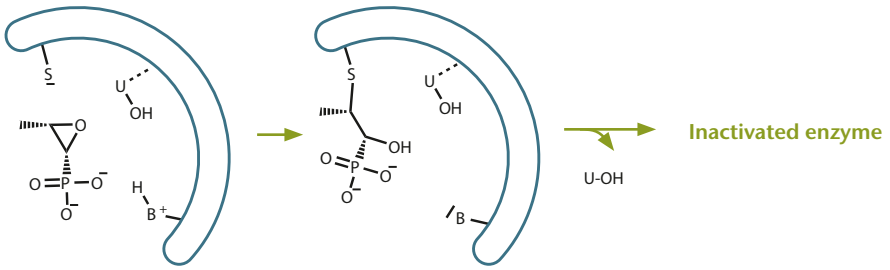


Figure 2: The alkylation of a cysteine residue at the active site of bacterial UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) inactivates the enzyme. U-OH: UDP-N-acetylglucosamine. B: Proton acceptor (modified from Woodruff et al. [353]).

Fosfomycin inhibits bacterial cell wall synthesis at an earlier stage than β-lactam antibiotics or glycopeptides, which inhibit bacterial transpeptidases and the formation of the murein net, respectively (Kahan *et al.* [164]). As its action takes place in the cytosol, fosfomycin must be transported into bacteria in order to be effective. Two major fosfomycin transport pathways have been described (Figure 3):

a) The facultative hexose monophosphate transport system (*UhpT*), which depends on the presence of glucose-6-phosphate (Lin [200]).
b) The L-α-glycerophosphate transport system (*GlpT*) which is induced by glyceraldehyde-3-phosphate (Lin [200]).

Further possible substrate-specific transport mechanisms (*OprO* and *OprP*) have recently been found in *P. aeruginosa* (Citak *et al.* [63]). Fosfomycin appears to be more effective under acidic or anaerobic conditions, which are commonly found in inflamed areas (Martín-Gutíerrez *et al.* [215], Hamilton-Miller [140]).

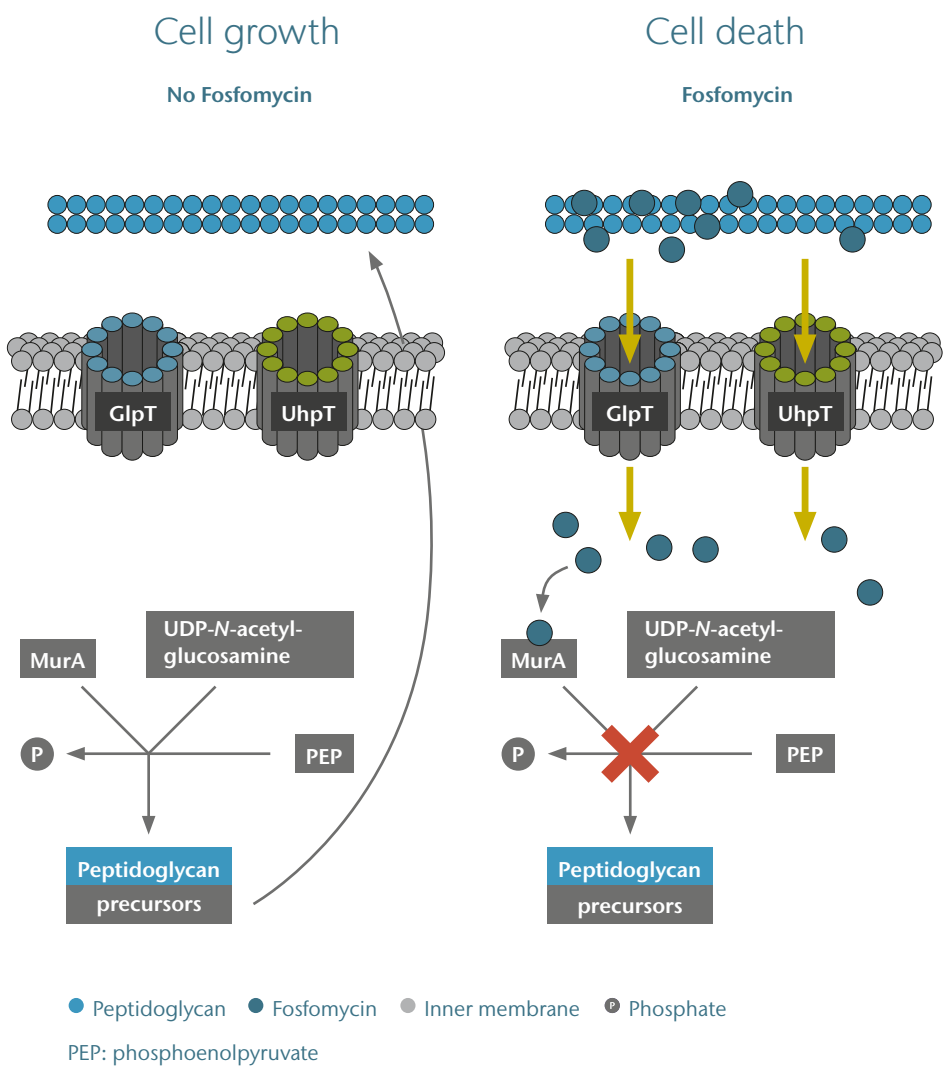


Figure 3: Fosfomycin transport mechanisms and mode of action (from Castañeda-Garcia et al. [59]).

2.4 Pharmacological profile

2.4.1 Pharmacokinetics

- Fosfomycin does not bind to plasma proteins.
- The apparent volume of distribution (V_d) is approximately 0.3 L/kg, suggesting virtually complete distribution into the tissue fluid space.
- Fosfomycin has a predictable, dose-proportional pharmacokinetic profile.
- Fosfomycin is not metabolised.
- Fosfomycin achieves excellent tissue penetration.
- Fosfomycin is primarily excreted in unchanged form by the kidneys.
- No therapeutic drug monitoring is required for fosfomycin.

2.4.1.1 Absorption, metabolism and excretion

Fosfomycin disodium is administered intravenously, its bioavailability is therefore (by definition) 100%. Oral fosfomycin formulations (fosfomycin trometamol) have bioavailabilities of approximately 30 to 50%, depending on fasting or feed conditions, with maximum concentrations being reached after about 2 h (Borsa *et al.* [49], Wenzler *et al.* [348]). Due to the low bioavailability of oral fosfomycin, product profiles and treatment indications vary substantially between the oral and the intravenous form. This monograph refers only to intravenous (i. v.) fosfomycin.

No fosfomycin metabolites have so far been identified in either plasma, saliva or urine. Hence, about 80–90% of the administered dose is excreted in the active form, primarily by the kidneys via glomerular filtration (Kirby [178], Wenzler *et al.* [348]). The largest proportion of this excretion occurs within 12 h post-dose. Following administration of a single dose of 8 g i. v. fosfomycin, approximately 6.4 g is recovered unchanged in the urine within 48 h (Figure 4). High urine fosfomycin concentrations can therefore be achieved (Wenzler *et al.* [348]).

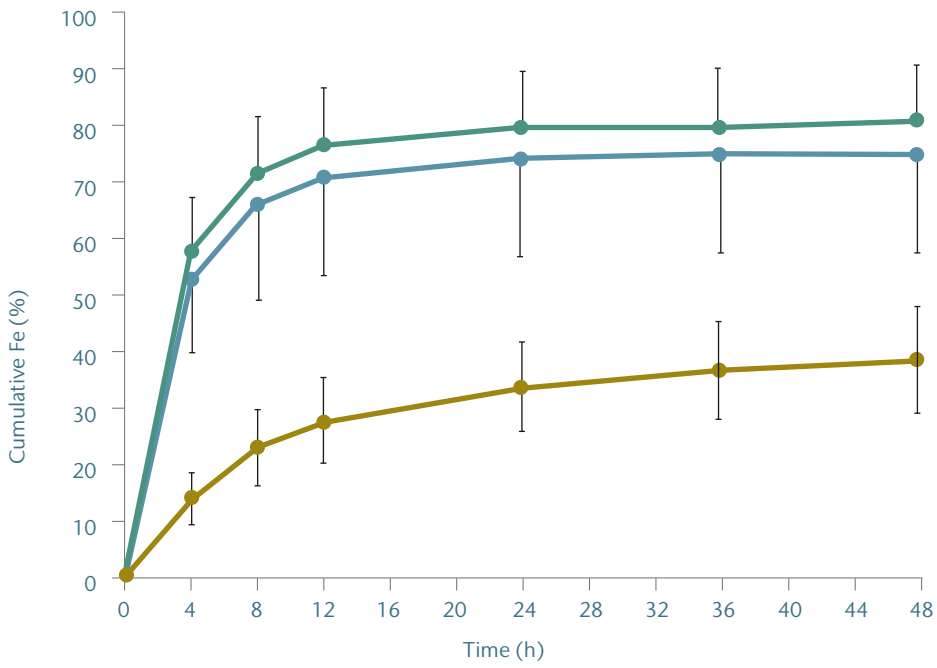


Figure 4: Mean (± SD) cumulative fraction (Cumulative Fe (%)) of the fosfomycin dose excreted in urine over time following oral and intravenous administration. Intravenous administration of 1 g is illustrated by open circles and a dashed line, and administration of 8 g is illustrated by open diamonds and a dashed line. Oral administration is illustrated by filled circles and a solid line (Wenzler et al. [348]).

2.4.1.2 Intracellular activity

- Fosfomycin enhances intracellular killing.

Fosfomycin is able to penetrate into human lymphocytes, where it takes full effect against pathogens that have survived initial phagocytosis by neutrophil leukocytes. This effect is especially important for persistent infections with staphylococci, where antibiotics with intracellular activity such as fosfomycin have a significant advantage over β-lactams and glycopeptides (Figure 5; Trautmann *et al.* [331]). A recent report explored the synergistic effects of fosfomycin and the host immune system in greater depth: Fosfomycin not only enhanced phagocytosis and intracellular killing by phagocytes, but also enhanced killing by macrophages and neutrophils mediated by extracellular traps (so called ETosis; Shen *et al.* [302]). In addition, Shen's group also analysed the molecular mechanisms of intracellular killing and reported that fosfomycin increased killing mediated by reactive oxygen species and hydroxyl radicals (Shen *et al.* [302]).

2.4.1.3 Pharmacokinetics in healthy individuals

- Fosfomycin distributes exclusively into the extracellular fluid.

The apparent volume of distribution (V_d) is approximately 0.3–0.4 L/kg, suggesting virtually complete distribution of fosfomycin into the extracellular fluid (Cadorniga *et al.* [55], Frossard *et al.* [112], Goto *et al.* [123], Wenzler *et al.* [348]). A summary of the main pharmacokinetic (PK) parameters of fosfomycin is presented in Table 2.

Table 2: Mean plasma concentrations and pharmacokinetic data for intravenous fosfomycin in healthy adults given single doses as indicated.

	Single intravenous dose					
	0.5 g (*n* = 6) [55]	40 mg/kg (*n* = 7) [123]	1 g (*n* = 27) [348]	2 g (*n* = 4) [178]	4 g (*n* = 6) [112]	8 g (*n* = 27) [348]
C_{max} (mg/L)	29.2	259	44	88	202	370
V_d (L)	20.9	0.34[a]	30	22	25	32
AUC (mg·h/L)	–	291	120	ND	443	1 060
$T_{½}$β (h)	2.04	2.2	2.4	1.5–2	1.8	2.8
CL_{tot} (L/h/kg)	–	0.14	0.12	–	0.12	0.11

C_{max}: Maximum observed concentration; V_d: Volume of distribution; $T_{½}$ β: Elimination half-life in β phase; AUC: Area under the curve; CL_{tot}: Total clearance; ND: Not determined. [a]Value in L/kg.

Figure 6 illustrates simulated time vs. concentration profiles for intravenous fosfomycin in healthy volunteers based on the pharmacokinetic parameters first published by Frossard *et al.* [112]. The impact of different dosing schemes is also illustrated, and a minimum inhibitory concentration (MIC) of 32 mg/L is identified as an important clinical breakpoint for *S. aureus* and *Enterobacterales*.

Extra- and intracellular activity of antibiotics

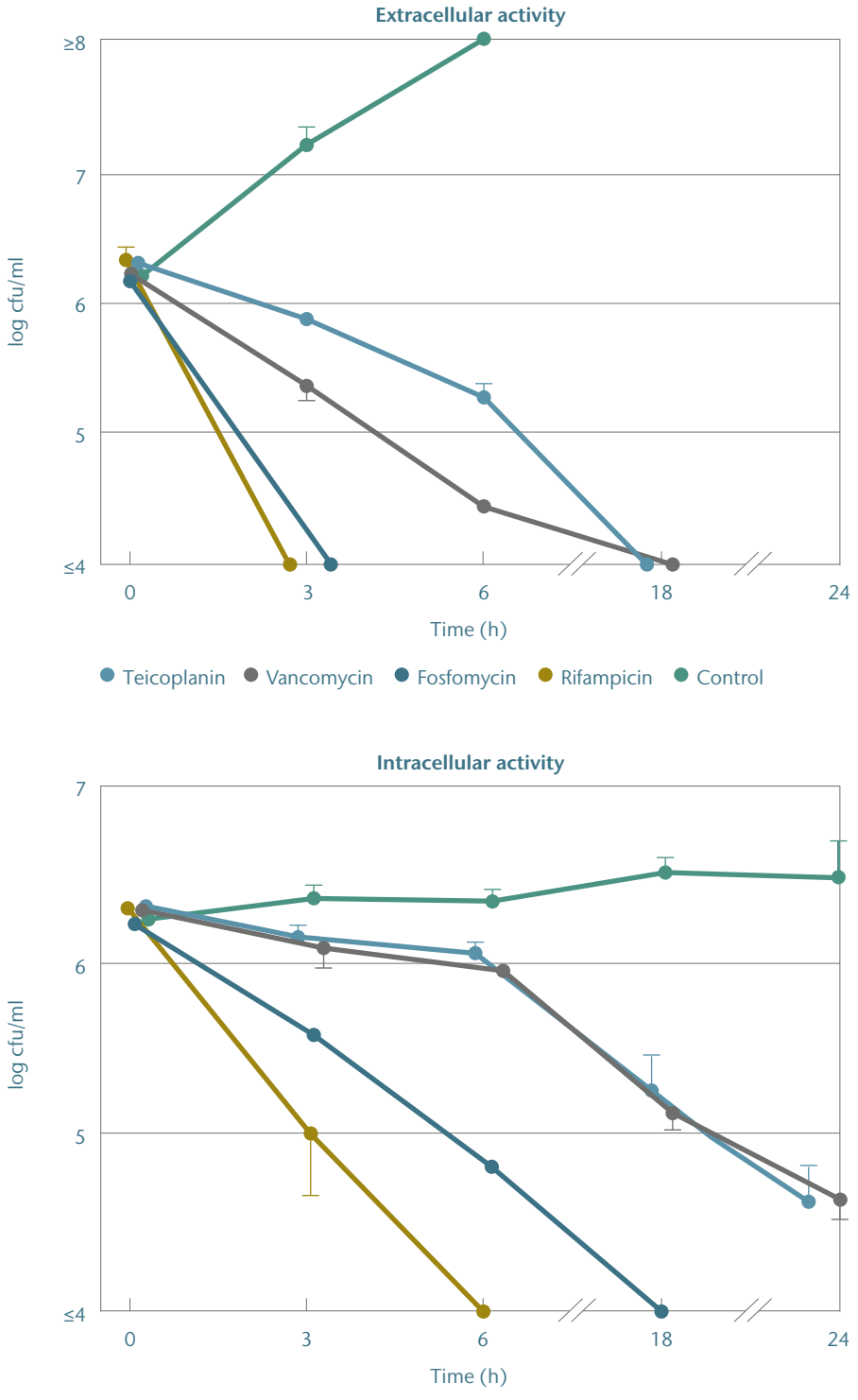


Figure 5: Difference between the extra- and intracellular activities of various antibiotics against S. aureus isolates (modified from Trautmann et al. [331]).

Modelled plasma pharmacokinetics for fosfomycin

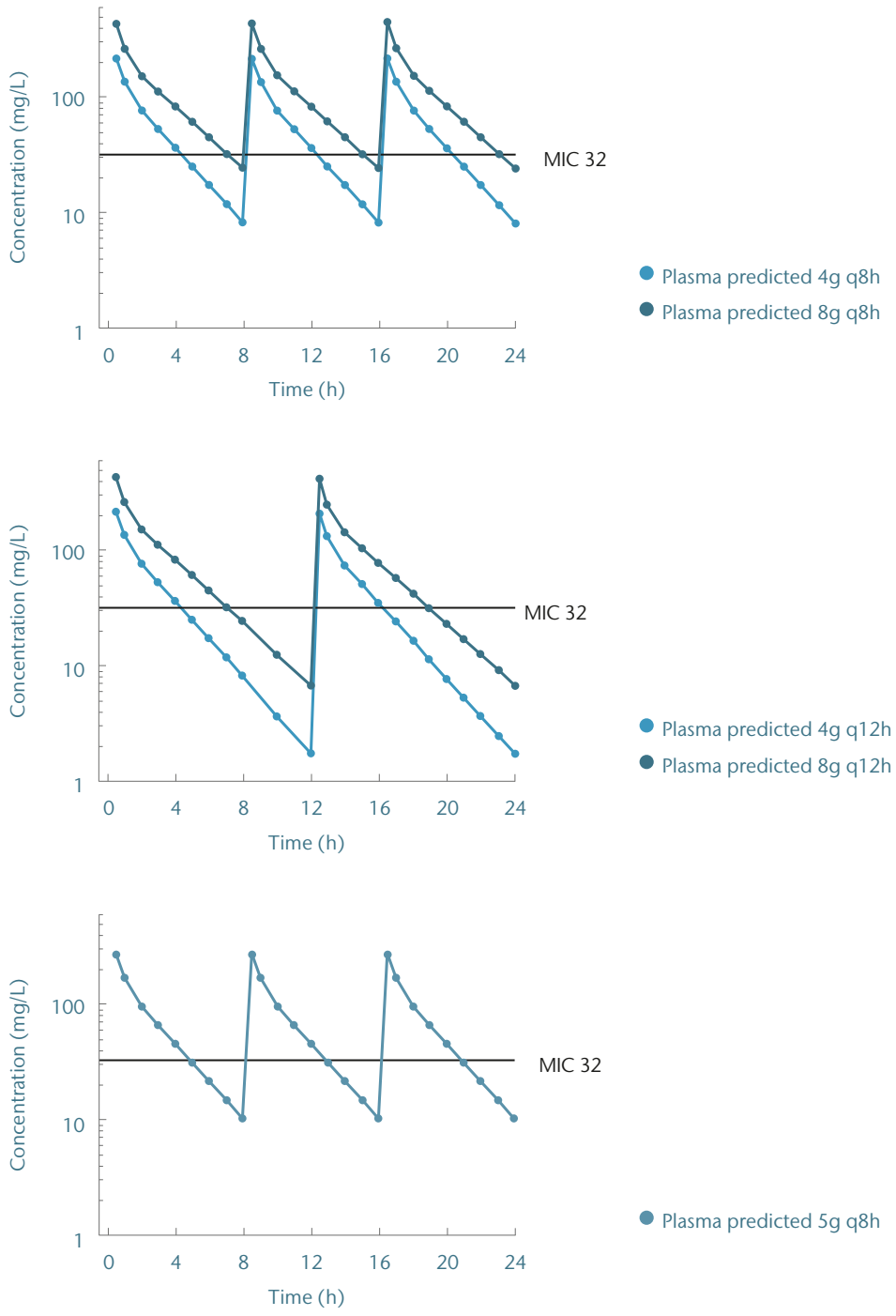


Figure 6: Mean simulated plasma concentration vs. time curves of intravenous fosfomycin using different doses and dosing schemes. Data are based on the pharmacokinetic data reported by Frossard et al. [112] for healthy volunteers. Dose is expressed as grams per time interval, e. g., 5 g q8h (every 8 hours).

2.4.1.4 Pharmacokinetics in special populations

Neonates and children

The pharmacokinetic parameters of fosfomycin have been determined in children, infants and neonates after single intravenous doses of 25–50 mg/kg (Table 3). Elimination half-lives in healthy children are generally shorter than in adults, but a considerable increase in elimination half-life is observed in neonates due to incomplete renal development in this group. Consequently, elimination of fosfomycin is more extensive in children than in new-borns (Traunmüller *et al.* [329]).

Table 3: Mean plasma concentrations and pharmacokinetic data for fosfomycin in neonates, infants, and children (Traunmüller *et al.* [329], Obiero *et al.* [246]).

Age	*N*	Dose (mg/kg)	C_{max} (mg/L)	$T_{½}$ β (h)	V_d (L/kg)	CL (mL/min/173 m²)
5.6 ± 1.7 yr	5	25[a]	58 ± 15[a]	0.9 ± 0.2	0.32 ± 0.09	4.3 ± 1.2b
5.3 ± 0.8 yr	10	25	102 ± 15	1.6 ± 0.3	≈0.28	112 ± 17
6.1 ± 1.0 yr	10	50	194 ± 53	1.7 ± 0.2	≈0.31	106 ± 25
Full-term neonates	5	25	62 ± 18[c]	2.4 ± 0.5	≈0.34	47 ± 17
Full-term neonates (week 38–40)	120	100 (bid)	202 (7–576)	5.2	≈0.39	0.14[d]
Pre-term neonates	5	25	62 ± 18[c]	2.8 ± 0.5	≈0.41	40 ± 10
Pre-term neonates (1–3 d)	6	50	99 ± 11	7.0	ND	15.5 ± 8.2[c]
Pre-term neonates (20–34 d)	5	50	99 ± 11	4.9	ND	19.2 ± 7.3[c]

ND: Not determined; C_{max}: Maximum observed concentration; V_d: Volume of distribution; $T_{½}$β: Plasma half-life in β phase; CL: Clearance; *N*: Number of patients.

[a]Infusion over 1 h; [b]Values expressed in mL/min/kg; [c]Values expressed as creatinine clearance; [d]L/h.

Critically ill patients with sepsis

Data on the plasma pharmacokinetics of fosfomycin in critically ill patients are limited. Joukhadar *et al.* published data on a single intravenous dose of 8 g in 9 critically ill adult patients with severe sepsis (Table 4) and noted a greater apparent volume of distribution in septic patients, reflecting interstitial fluid oedema (Joukhadar *et al.* [161]). More recent studies using population pharmacokinetic analysis in critically ill patients have confirmed this initial finding of a greater volume of distribution, as well as a smaller mean clearance, and also noted significant pharmacokinetic variability due to the heterogeneity of critically ill patient populations (Parker *et al.* [255]).

Table 4: Plasma pharmacokinetics of fosfomycin in 9 septic adult ICU patients following a single i. v. dose of 8 g (mean ± SD) (Joukhadar *et al.* [161]).

C_{max} (mg/L)	T_{max} (h)	$T_{½}$ β (h)	CL_{tot} (L/h)	$AUC_{0–4}$ (mg × h/L)	V_d (L)
357 ± 28	0.4 ± 0.1	3.9 ± 0.9	7.2 ± 1.3	721 ± 66	31.5 ± 4.5

C_{max}: maximum observed concentration; T_{max}: Time at which maximum concentration is observed; V_d: volume of distribution; $T_{½}$β: elimination half-life in β phase; AUC: area under the curve.

Patients with liver failure

Fosfomycin exhibits minimal biliary elimination and does not undergo enterohepatic recirculation (Kirby [178]). Therefore no dose adjustment is required in this patient group and there is no contraindication.

Patients with kidney failure and patients on renal replacement therapy

The primary route of elimination of fosfomycin is via the kidneys (Goto *et al.* [123], Kirby [178], Cadorniga *et al.* [55], Iwai *et al.* [156]). In patients with kidney failure, fosfomycin concentrations and elimination rates correlate with serum creatinine and creatinine clearance values (Gobernado *et al.* [120], Fernandez Lastra *et al.* [99], Neuman *et al.* [240]). Thus, patients presenting with severe renal failure require dose adjustments, in particular if they show a creatinine clearance of less than 40 mL/min (Fernandez Lastra *et al.* [99], Gallego *et al.* [115], Bergan [38]). See Section 2.4.5 (Dosing and administration of fosfomycin) for more detail.

Haemodialysis

Fosfomycin is well cleared by haemodialysis: Studies in patients without infection showed that 70–80% of fosfomycin doses of 1–2 g can be cleared during a 6-hour session of haemodialysis (Dalet *et al.* [71], Revert *et al.* [274]). This corresponds to a plasma elimination half-life of 2.2–2.8 h, comparable to that found in healthy adults. Furthermore, pharmacokinetic profiles for haemodialysis patients receiving 2 g of fosfomycin before or after each session have been determined (see Table 5; Bouchet *et al.* [50]). A recent investigation described higher fosfomycin clearance in two critically ill patients undergoing intermittent or extended haemodialysis with clearance rates of 75 and 116 mL/min respectively (Schmidt *et al.* [298]).

Table 5: Main pharmacokinetic parameters of fosfomycin (2 g single dose) in patients undergoing haemodialysis (Bouchet *et al.* [50]). Data presented as means.

Study group	$T_{½}$ β (h)	$AUC_{0–inf}$ (mg × h/L)	CL (mL/min)	V_d (L)
Dose 15 min before HD (n = 6)	4.2	540.2	64.7	23.6
Dose after HD (n = 6)	48.8	9 021.8	<5	ND

HD: Haemodialysis; V_d: Volume of distribution; $T_{½}$β: Plasma half-life in β phase; CL: Clearance; AUC: Area under the curve; ND: Not determined.

Haemofiltration

Two studies have determined pharmacokinetic parameters in anuric patients receiving either haemofiltration (HF) or continuous veno-venous HF (CVVHF) and given single i. v. doses of between 1.6 g and 8 g fosfomycin. Table 6 summarises the main serum pharmacokinetic parameters, indicating similar percentages of drug removal (> 70%) as for haemodialysis.

Table 6: Serum pharmacokinetics of fosfomycin in patients undergoing renal replacement therapy (single i. v. dose).

Therapy	Membrane surface (m^2)	Dose (g)	$T_{½}$ β (h)	CL (mL/min)	V_d (L)	Drug removal (%)
4 h HF (n = 10)	0.3	1.6–2.1	4.0	91.9	ND	ND
CVVHF[a] (n = 10)	1.2	8	12.1	106.7	33.7	76.7

$T_{½}$β: Plasma half-life in β phase; CL: Clearance; V_d: Volume of distribution. HF: Haemofiltration; CVVHF: Continuous veno-venous haemofiltration; ND: Not determined. Data from Fernández-Lastra *et al.* [100] and Gattringer *et al.* [117]. [a]Values obtained from the "arterial" port of the HF device.

Morbidly obese patients (BMI ≥ 38)

The pharmacokinetics of fosfomycin in obese versus non-obese patients both undergoing surgery after administration of 8 g fosfomycin are characterised by slightly lower peak plasma concentrations and higher volume of distribution in the former group. However, the drug concentration in tissue was nearly halved in obese compared to non-obese patients (Figure 7; Dorn *et al.* [84]).

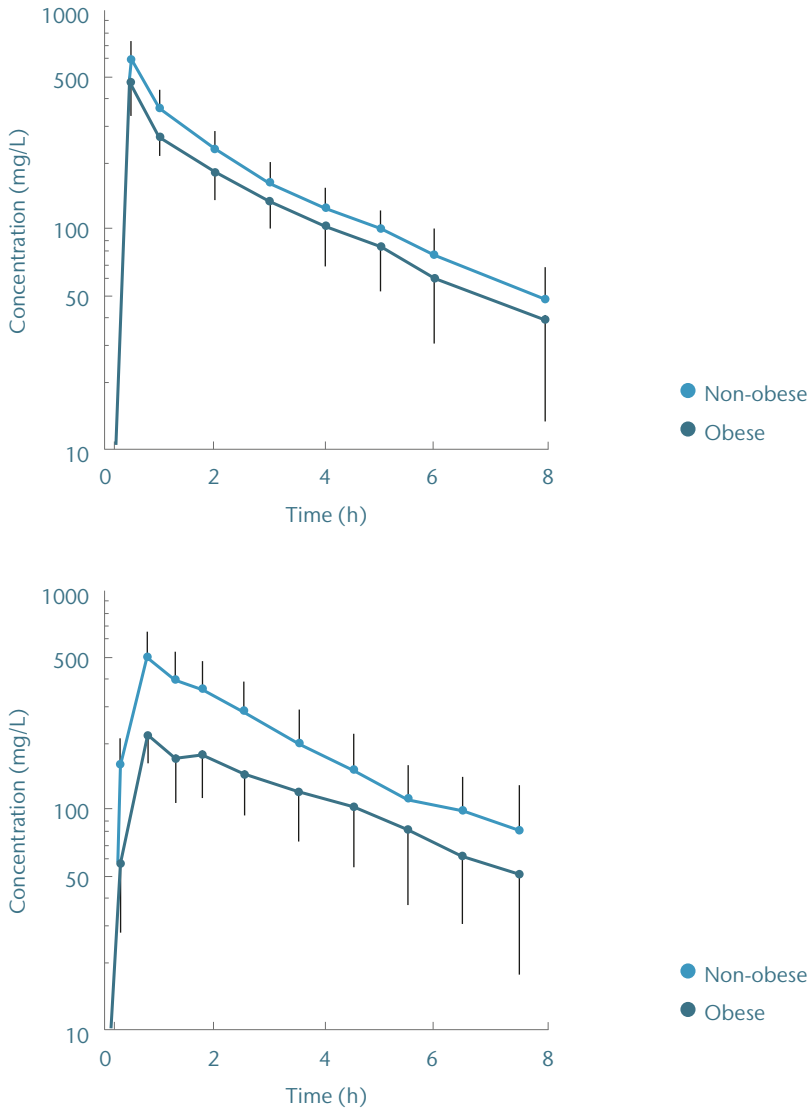


Figure 7: Concentration vs. time course (mean and SD) of fosfomycin in plasma (a) and subcutaneous tissue (b) in obese and non-obese surgical patients following a single intravenous short infusion of 8 g of fosfomycin (Dorn et al. [84]).

2.4.1.5 Protein binding, tissue distribution and penetration

The protein binding of fosfomycin is negligible (0–2%), making the vast majority of the administered dose actively available. Fosfomycin displays excellent penetration into a variety of compartments including skin and soft tissues, muscle, lung tissue, bone, eye, heart, and abscesses, as well as body fluids such as bronchial secretions, pleural effusions, cerebrospinal fluid, and bile (Figure 8; Roussos *et al.* [286]).

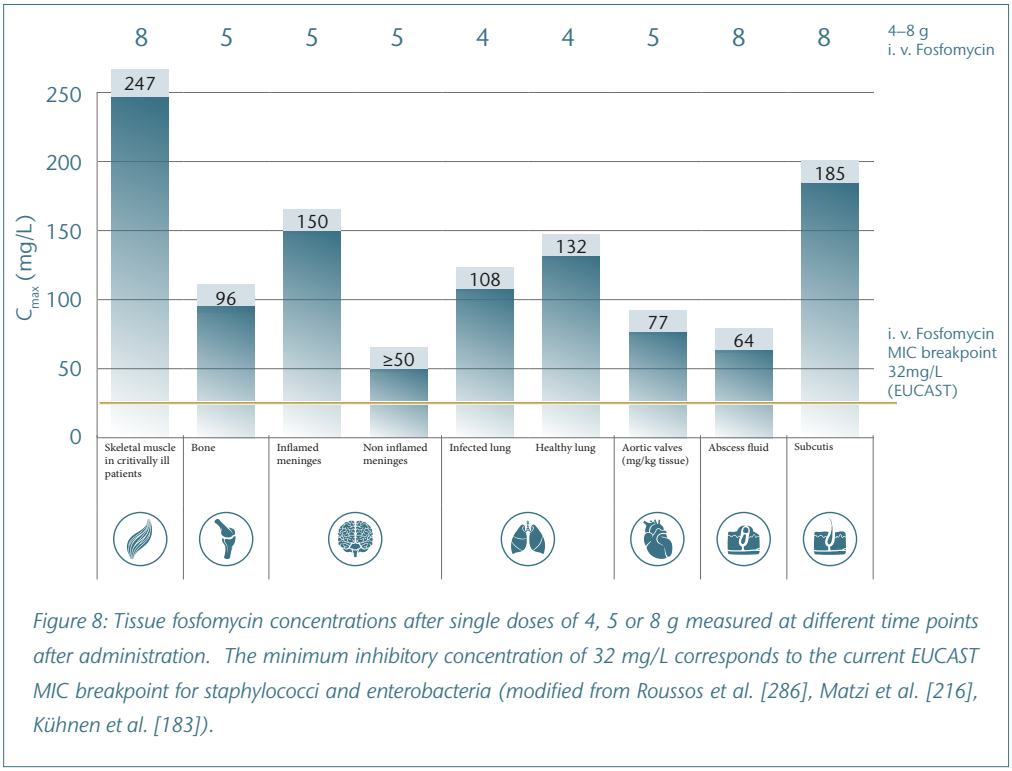


Figure 8: Tissue fosfomycin concentrations after single doses of 4, 5 or 8 g measured at different time points after administration. The minimum inhibitory concentration of 32 mg/L corresponds to the current EUCAST MIC breakpoint for staphylococci and enterobacteria (modified from Roussos et al. [286], Matzi et al. [216], Kühnen et al. [183]).

Lung tissue and bronchial secretions

Data on fosfomycin concentrations in lung tissue and bronchial secretions are available both from homogenised biopsies and microdialysate samples. In a study on lung biopsies, patients undergoing lung surgery received 5 g fosfomycin as a brief infusion, and lung tissue fosfomycin concentrations were found to be 119 mg/L and 49 mg/L at 1 h and 6.5 h after administration, respectively, corresponding to 70–80% of the plasma concentration (Adam *et al.* [3]).

Matzi *et al.* used microdialysis to compare fosfomycin concentrations between healthy and infected lung tissues in 7 adult patients and reported no differences between the pharmacokinetic profiles of both tissue types (Matzi *et al.* [216]). The authors further concluded that high-dose regimens of up to 24 g/d might be advisable in severe lung infections caused by less susceptible pathogens (Figure 9).

Concentrations of fosfomycin in plasma and lung

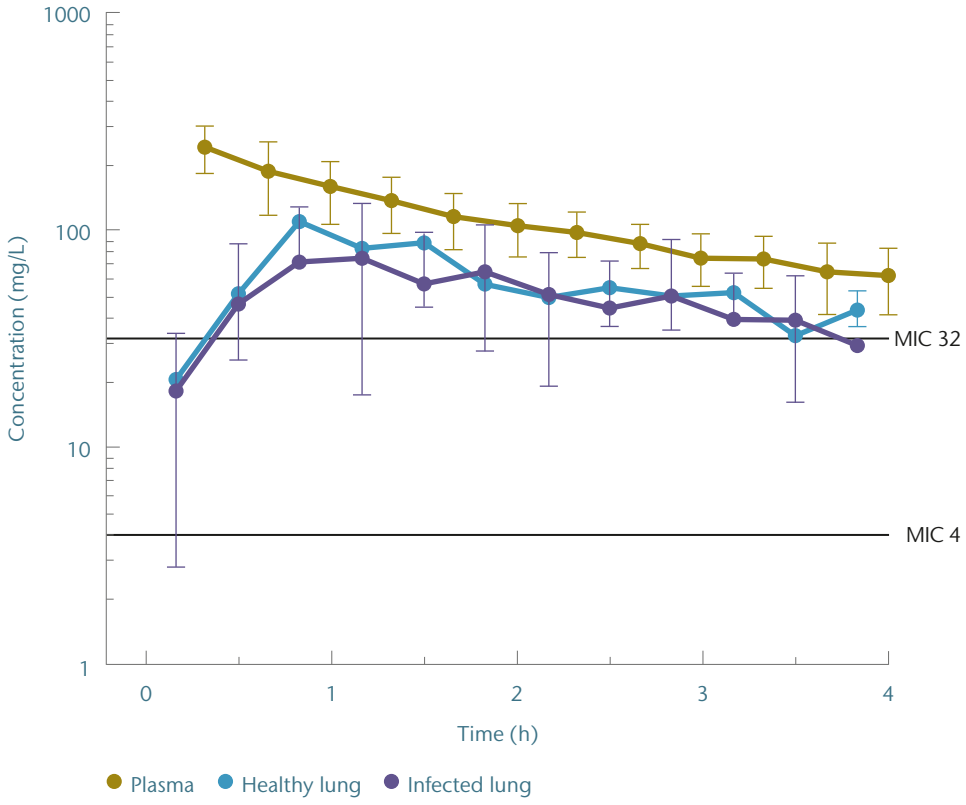


Figure 9: Pharmacokinetic profiles of fosfomycin in plasma and lung tissue of patients with severe lung infection and sepsis following a single intravenous dose of 4 g (n = 7). Lung concentrations were measured by in vivo microdialysis (mean ± SD). Solid line: MIC 32 mg/L corresponds to the current EUCAST breakpoint for staphylococci and enterobacteria (modified from Matzi et al. [216]); MIC 4 mg/L corresponds to the MIC90 determined for ESBL-producing E. coli and MRSA (PEG [256]).

Sputum fosfomycin concentrations in patients with bacterial respiratory tract infections have also been investigated. Concentrations ranged from 12 to 14 mg/L and were reached at 30 min after administration of 4 g (Berthelot *et al.* [40]) or 60 mg/kg (Bonora *et al.* [47]) fosfomycin.

Bone tissue

Fosfomycin also penetrates well into bone tissue, providing the rationale for its effectiveness in osteomyelitis and related diseases. Results from *in vitro* experiments indicate that fosfomycin may be adsorbed onto bone tissue components, particularly hydroxyapatite (Haag *et al.* [132], Wittmann [352], Bauernfeind *et al.* [37]). Sirot *et al.* detected fosfomycin concentrations of 8.2–19.6 mg/L in different bone tissues at 1–2 h after administration of 4 g fosfomycin (Sirot *et al.* [311]), whereas Meißner *et al.* reported more than tenfold higher concentrations (approx. 150 mg/L) in different bone types in patients at 1–2 h after administration of 10 g fosfomycin (Meißner *et al.* [219]). It should be noted that concentration data from tissue biopsies represent the average of intra- and extracellular tissue compartments. Values may therefore be artificially increased by residual blood, and this may explain at least some of the observed variability.

In contrast, Schintler *et al.* used in *vivo* microdialysis to determine fosfomycin concentrations in macroscopic healthy metatarsal bone in patients scheduled for partial bone resection due to bacterial foot infection and osteomyelitis. Plasma and unaffected subcutaneous adipose tissue served as reference compartments (Schintler *et al.* [297]). Figure 10 illustrates the observed *in vivo* tissue penetration of fosfomycin and shows that equilibrium with the plasma concentration was established approximately 3 h after dosage.

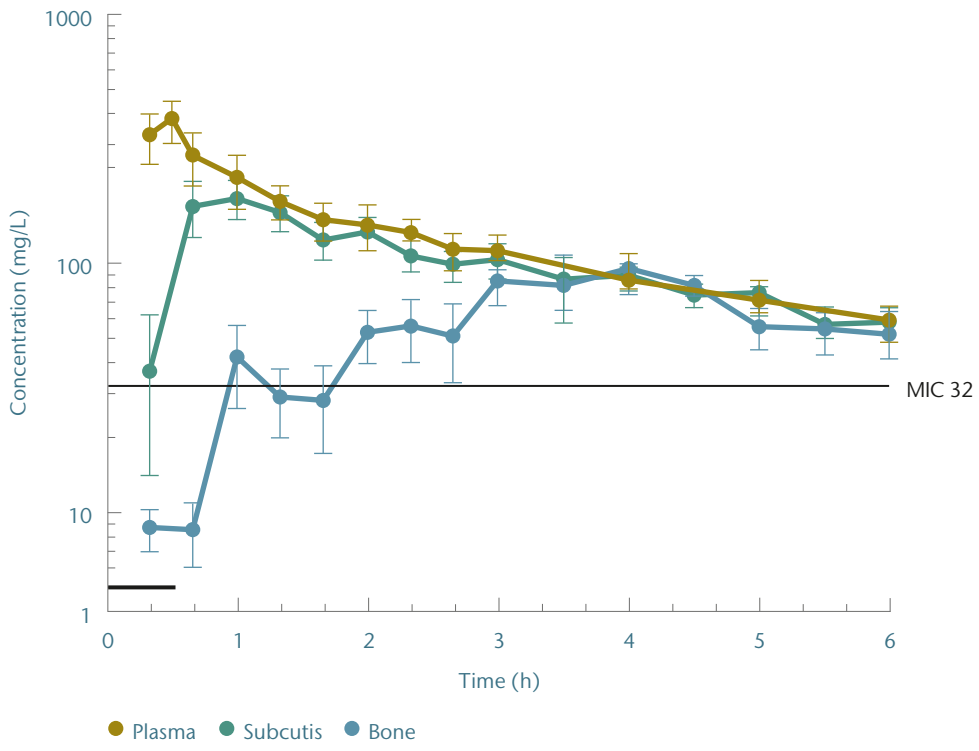


Figure 10: Pharmacokinetic profiles in plasma and target tissues in 9 elderly diabetics with bacterial foot infections following a single intravenous dose of 100 mg/kg of fosfomycin (mean ± SD). Tissue concentrations were measured by in vivo microdialysis. The solid line shows the infusion. MIC 32 mg/L corresponds to the current EUCAST breakpoint for staphylococci and enterobacteria (modified from Schintler et al. [297]).

CNS, cerebrospinal fluid and inflamed meninges

Penetration of hydrophilic antibiotics into intact meninges and the cerebrospinal fluid (CSF) is very limited. However, owing to its low molecular weight, fosfomycin is an exception to this rule (Table 7). In a study of 50 accident patients receiving single intravenous fosfomycin doses of 70 mg/kg, CSF and venous blood were sampled at defined time points. The ratio of CSF and plasma concentrations was 0.04 after 2 h, but gradually increased to 0.72 at 8 h post-dose. Complete CFS/plasma equilibrium was reached at approximately 10–12 h (Oellers *et al.* [248]).

The ability of fosfomycin to penetrate the intact blood/brain barrier was confirmed in another study in patients with ventricular drainage systems implanted for neurosurgical indications (Pfeifer *et al.* [263]). Total CSF protein concentrations and cell counts were normal,

indicating the absence of inflammation. Patients were divided into two groups receiving either 5 g (n = 17) or 10 g (n = 4) fosfomycin as a 30-min intravenous infusion. CSF fosfomycin concentrations showed a plateau between 3 and 6 h, followed by an elimination phase with a half-life of approximately 6 h. Further experiments using multiple doses – 3× 5 g fosfomycin daily – showed the CSF concentration increasing to 50 mg/L (Pfeifer *et al.* [263], Kühnen *et al.* [183]; reports published in 1985 and 1987, respectively).

In a more recent study, reported in 2004, Pfausler *et al.* collected data from patients with drain-associated ventriculitis treated with 3× 8 g fosfomycin daily. The authors observed good coverage of susceptible bacteria in cerebrospinal fluid and confirmed previous evidence on the penetration characteristics of fosfomycin. They also noted incomplete equilibration between plasma and cerebrospinal fluid, which may indicate the operation of active transport mechanisms such as the P-glycoprotein system, preventing equilibrium from being reached (Pfausler *et al.* [262]; see Figure 11). However, the detailed mechanism for fosfomycin transport across the blood/brain barrier is not yet understood.

Table 7: Penetration of antibiotics into the CNS (cerebrospinal fluid (CSF)).

Antibiotic (class)	**AUC_{CSF}/AUC_{serum} (%)**		**Reference**
	Non- or moderately inflamed meninges	**Strongly inflamed meninges**	
Penicillin	2	20	Nau [237]
Cephalosporin	0.7–1	15	Nau [237]
Carbapenem	20	30	Nau [237]
Vancomycin	14–18	30	Nau [237]
Daptomycin	0.8	n/a	Kullar [184]
Fosfomycin	**27**	**50–70[a]**	**Pfausler [262], Friedrich [111]**
Linezolid	90	n/a	Nau [237]

n/a: not available.

[a]Ratio C_{CSF}/C_{serum} 3 h, 8 h post-infusion, dosage 5 g q8h, steady-state C_{CSF} reached after approximately 3 h (Friedrich *et al.* [111]).

Additional studies showed that inflammation further increased the penetration rate of fosfomycin across the meninges. At the steady state, patients with meningitis had CSF concentrations 4–7 times higher than patients without meningeal inflammation (see Figure 12; Friedrich *et al.* [111]). Studies in paediatric patients showed that fosfomycin concentrations in the CSF were much larger during the acute phase of the meningitis than in the absence of inflammation (3.7–11% of measured plasma values determined in 22 paediatric patients, including one neonate) (Llorens *et al.* [205]). Thus, multiple studies have strengthened the current view that fosfomycin has excellent penetration characteristics combined with a high bactericidal activity, which is of great clinical value for CNS infections (Drobnic *et al.* [86], Sicilia *et al.* [306], Tsegka *et al.* [332]).

Overall, fosfomycin is a unique antibiotic with excellent tissue penetration characteristics due to its low molecular weight. Its pharmacokinetic profile makes it an excellent treatment option for challenging infections.

Concentrations of fosfomycin in plasma and CSF

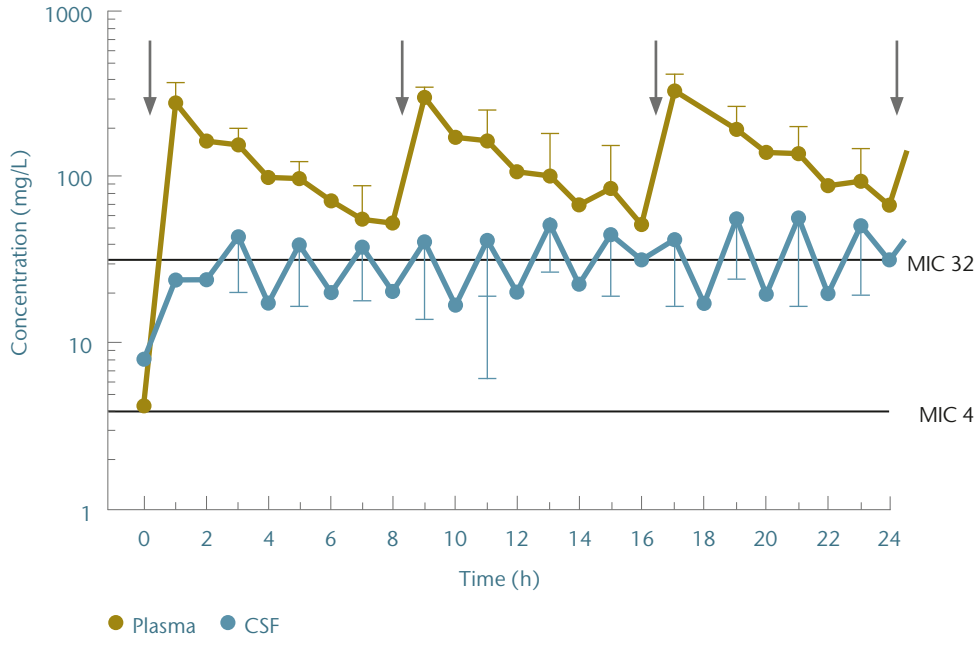


Figure 11: Concentration vs. time profiles of fosfomycin in plasma and cerebrospinal fluid (CSF) in neurointensive care patients (n = 6). Arrows show fosfomycin doses (3× 8 g/d) (modified from Pfausler et al. [262]); MIC 4 mg/L corresponds to the MIC90 for ESBL-producing E. coli and MRSA (PEG [256]).

Linear pharmacokinetics of fosfomycin

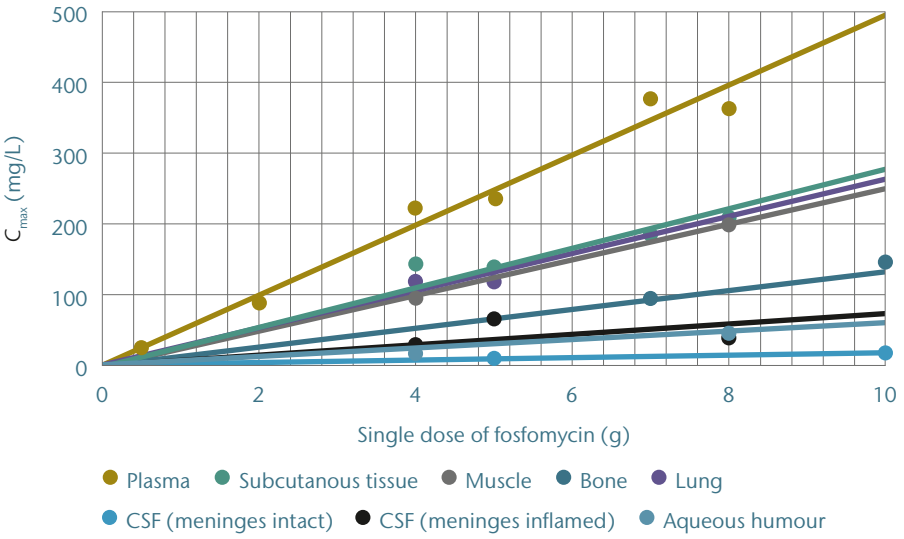


Figure 12: Pharmacokinetic behaviour of fosfomycin. Relationship between single doses in grams and maximum achievable concentrations (mg/L) in the plasma and various tissue types.

2.4.2 Pharmacodynamics

- Fosfomycin displays a broad antimicrobial spectrum.
- Its activity includes both gram-positive and gram-negative pathogens.
- Activity against a variety of problem bacteria including MRSA, VRE, ESBL- and carbapenemase-producing enterobacteria (all Ambler classes), and multidrug-resistant *Pseudomonas aeruginosa*.
- High activity against biofilms.
- Synergistic or additive effects with all antibiotic classes.
- Reno-protective effect if combined with nephrotoxic drugs.
- Impact of resistance against fosfomycin in daily clinical routine remains low.

2.4.2.1 Spectrum of antimicrobial activity

Fosfomycin displays bactericidal activity against a wide range of gram-positive and gram-negative bacteria, including problem bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant enterococci, and multidrug-resistant enterobacteria (Falagas *et al.* [97]). Table 8 shows an overview of susceptible species and includes the organisms relevant to the approved indications for fosfomycin.

Susceptibility data of the most important pathogens including the test method used gathered from several studies around the world are summarised in Table 9. Most of the fosfomycin MIC50/90 values of clinically relevant pathogens like *S. aureus* and *Enterobacterales* are below the clinical breakpoint of 32 mg/L, indicating stable susceptibility in several regions of the world. *P. aeruginosa* generally show higher fosfomycin MICs. Many of the *P. aeruginosa* isolates had MICs in the vicinity of the epidemiological cut-off of 128 mg/mL (Table 9).

Table 8: *In-vivo* activity spectrum of fosfomycin.
Commonly susceptible species
Aerobic gram-positive microorganisms
Staphylococcus aureus
Aerobic gram-negative microorganisms
Citrobacter freundii
Citrobacter koseri
Escherichia coli
Haemophilus influenzae
Neisseria meningitidis
Salmonella enterica
Anaerobic microorganisms
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Species in which acquired resistance may be a problem
Aerobic gram-positive microorganisms
Staphylococcus epidermidis
Streptococcus pneumoniae
Enterococcus spp.
Aerobic gram-negative microorganisms
Enterobacter cloacae
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella pneumonia
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens
Anaerobic gram-positive microorganisms
Clostridium spp.
Inherently resistant species
Aerobic gram-positive microorganisms
Staphylococcus saprophyticus
Streptococcus pyogenes
Aerobic gram-negative microorganisms
Legionella pneumophila
Morganella morganii
Stenotrophomonas maltophilia
Anaerobic gram-negative microorganisms
Bacteroides spp.
Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.

Table 9: *In-vitro* fosfomycin MICs for important bacterial pathogens. The EUCAST clinical breakpoint for susceptibility assessment for *Enterobacterales* and *Staphylococcus* spp. is 32 mg/L.

Pathogen	Fosfomycin MIC50/90 (mg/L)	Method of MIC testing[a]	Geographic region, publication year [Reference]
Gram-positive bacteria			
Staphylococcus aureus	8/16 4/16 1/2 4/8 8/16	AD AD BMD AD BMD	USA, 2005 [45] Europe, 2013 [93] Germany, 2016 [256] USA, 2019 [103] Italy, 2018 [308]
Enterococcus faecalis	32/64 2/8 64/128	BMD BMD E-test	Germany, 2016 [256] Italy, 2018 [308] Germany, 2019 [273]
Enterococcus faecium	64/64 8/16	BMD BMD	Germany, 2016 [256] Italy 2018 [308]
Gram-negative bacteria			
Escherichia coli	2/8 4/16 1/4 0.5/1 1/1 0.5/1 ≤1/4	AD AD BMD AD AD AD AD	Spain, 2004 [8] Europe, 2013 [93] Germany, 2016 [256] USA, 2017 [103] USA, 2018 [304] Eastern Europe[b], 2018 [305] Canada, 2014 [172]
Klebsiella pneumoniae	32/>128 16/64 16/64 4/16 8/64 8/64	AD AD BMD AD AD AD	Spain, 2004 [14] Europe, 2013 [145] Germany, 2016 [271] USA, 2019 [103] USA, 2018 [304] Eastern Europe[b], 2018 [305]
Serratia marcescens	4/16 16/32 8/16	AD BMD AD	Europe, 2013 [93] Germany, 2016 [256] USA, 2019 [164]
Proteus mirabilis	4/32 4/64 1/8 2/16 2/32	AD BMD AD AD AD	Europe, 2013 [93] Germany, 2016 [256] USA, 2019 [103] Croatia, 2018 [41] USA, 2018 [304]
Enterobacter spp.	32/128 16/128 8/16	BMD AD AD	Germany, 2016 [256] USA 2018 [304] USA, 2019 [103]
Citrobacter spp.	16/64 0.125/0.25 1/4 0.5/1 4/16	AD AD BMD AD AD	The UK, 2011 [295] Europe, 2013 [93] Germany, 2016 [256] USA, 2019 [103] Croatia, 2018 [41]

Pathogen	Fosfomycin MIC50/90 (mg/L)	Method of MIC testing[a]	Geographic region, publication year [Reference]
Gram-negative bacteria			
Pseudomonas aeruginosa	64/128 128/256 64/128 128/256 64/256	AD BMD AD AD AD	Europe, 2013 [93] Germany, 2016 [256] USA, 2019 [103] Croatia, 2018 [41] USA 2018 [304]
Acinetobacter baumannii	128/256 128/256 128/ N/A	BMD AD AD	Germany, 2016 [256] USA, 2019 [103] USA 2018 [304]

AD: Agar dilution method; BMD: Broth microdilution method.

[a]All MICs were determined in the presence of glucose-6-phosphate (25–50 mg/L). [b]Pooled data from Belarus, Croatia, Czech Republic, Hungary, Poland, Romania, Russia, and Slovakia.

Recent data from more than 1 400 gram-negative and 800 gram-positive clinical isolates collected during the SENTRY Antimicrobial Surveillance programme in US medical centres showed the potent activity of fosfomycin against these bacteria using an agar dilution technique. According to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint criteria, for example, 99% of the 102 *E. coli* isolates tested, 96% of the 100 *K. pneumoniae* isolates tested, 100% of the 103 *S. aureus* (MSSA) isolates tested, 99% of the 101 *S. aureus* (MRSA) isolates tested and 83.8% of the 105 coagulase-negative staphylococci tested (except *S. saprophyticus*) were sensitive to fosfomycin. In total, 94.9% of all *Enterobacterales*, including isolates with ESBL- and carbapenem-resistant phenotypes, were susceptible to fosfomycin. 95% of the 100 *P. aeruginosa* isolates tested had MIC ≤ 128 µg/mL (Flamm *et al.* [103]).

2.4.2.2 Activity of fosfomycin against 'problem' bacteria

Methicillin-resistant *Staphylococcus aureus* (MRSA)

The emergence of resistance to antibiotics in bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), has become a global threat, though recent prevalence has been declining. The prevalence of methicillin resistance among *S. aureus* is still quite high in Europe, ranging from 0% to >40%. The highest prevalence levels are seen in Romania, Malta, Portugal, Cyprus, Greece, and Italy (ECDC [91]; see Figure 13).

Because of its unique mechanism of action, fosfomycin is highly active against both methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) *Staphylococcus aureus* strains. MRSA often exhibits multidrug resistance to β-lactams and other groups of antibiotics and is coming to be recognised as a nosocomial problem bacterium. Resistance rates for fosfomycin (MIC > 32 mg/L) for both MSSA and MRSA strains have been found to be below 10% in several European regions, Canada and the United States (Hara *et al.* [141], Grif *et al.* [129], Iwantscheff [157], Graninger *et al.* [127], Van der Auwera *et al.* [339], Bogdanovich *et al.* [45], Scholz *et al.* [299], Falagas *et al.* [97], Maraki *et al.* [209], Witte [351], Del Valle *et al.* [77], Vardakas *et al.* [341], Zhanel *et al.* [358], Flamm *et al.* [103], Bielen *et al.* [41], Simonetti *et al.* [308]).

Vancomycin-resistant enterococci (VRE)

The rapid and continuous increase in the percentage of vancomycin resistance in *E. faecium* in the EU/EEA is a cause for concern. While vancomycin resistance in *E. faecalis* remains low

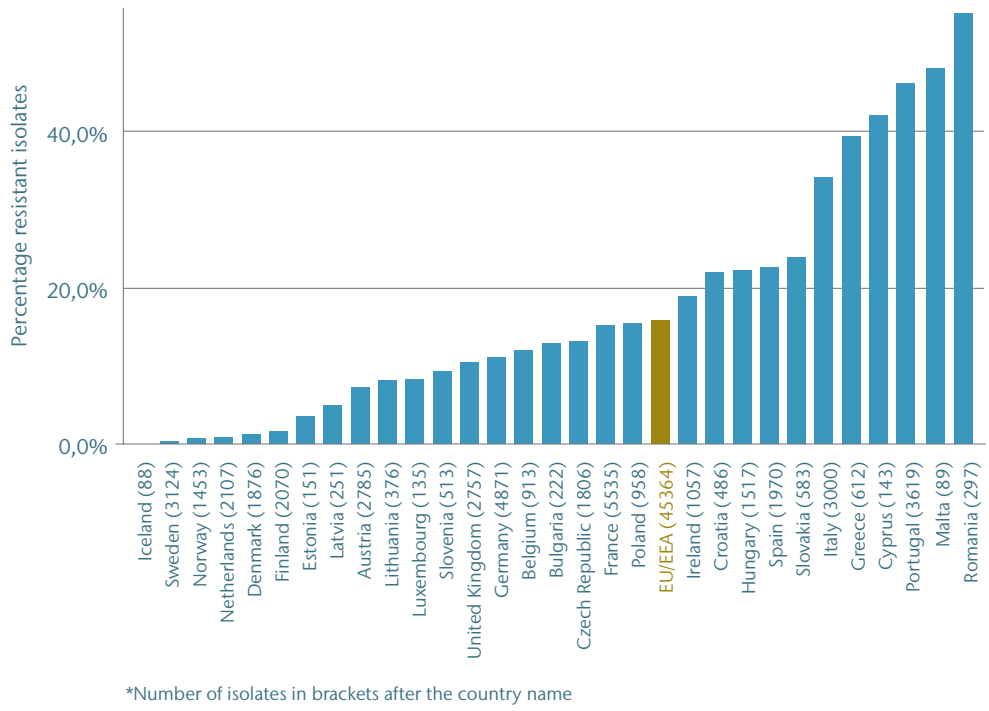


Figure 13: Methicillin resistance among Staphylococcus aureus isolates in participating countries of the European Centre for Disease Prevention and Control (ECDC) network; data from 2018 (ECDC [91]).

in most countries, vancomycin resistance in *E. faecium* was 17.3% in 2018, which represents a significant increase from 2015 when the corresponding value was 10.5%. National percentages ranged from 0.0% (Luxembourg) to 59.1% (Cyprus). Only 12 of the 30 reporting countries reported resistance percentages below 5% (ECDC [91]).

Fosfomycin is an effective alternative treatment for VRE, which constitute a major problem among nosocomial infections (Vardakas *et al.* [341]). In microbiological studies, fosfomycin has been reported to be effective against a variety of vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* isolates. At present, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has not set an official clinical breakpoint for *Enterococcus* spp. According to EUCAST fosfomycin MIC distributions, 89% of *Enterococcus faecium* (431/483 isolates, 1 observation) and 95% of *Enterococcus faecalis* isolates (1 581/1 666 isolates, 6 observations) could be considered susceptible, using the CLSI breakpoint of 64 mg/L (www.eucast.org). Data from the literature report overall susceptibility rates of VRE of 97% (Allerberger *et al.* [9]). Maraki *et al.* reported susceptibility rates of 91.9% for clinical urinary isolates of *Enterococcus faecalis* (Maraki *et al.* [209]). Among a collection of 112 VRE isolates from ICU patients at Turkish teaching hospitals, only 1 strain was resistant to fosfomycin (99.1% susceptibility; Iris *et al.* [155]). Other authors use even higher cut-off values of 128 mg/L for susceptibility assessment of enterococci (including VRE) towards fosfomycin that are well-established in clinical practise (Renz *et al.* [273]).

Multidrug-resistant enterobacteria

Organisms producing enzymes such as extended-spectrum β-lactamases (ESBL) or carbapenemases are clinically relevant and have become important players among antimicrobial-resistant organisms because of their broad resistance to many β-lactam antibiotics such as penicillins, cephalosporins and monobactams (and carbapenems in the case of carbapenemases). Reports from most infectious diseases societies including the WHO list multidrug-resistant enterobacteria like *Klebsiella* spp. and *Escherichia coli* as priority drug-resistant microbes against which new therapies are urgently needed. Both of these can cause important

Table 10: Susceptibilities of ESBL-producing enterobacteria to fosfomycin from Europe and North America.

First author, geographic region [Ref.]	Pathogen (number of isolates)	Years of collection	Source	Method (breakpoint[a])	Fosfomycin $MIC_{50/90}$ (mg/L)	Susceptibility rate[a] (%)
Falagas, Greece [95]	*Klebsiella pneumoniae* (30)	2006–2007	Clinical	Agar dilution (≤32 mg/L)	16/32	93.3
Falagas, Greece [96]	*Klebsiella pneumoniae* (10)	2007–2009	Clinical	Agar dilution (≤32 mg/L)	32/128	60.0
	Escherichia coli (24)	"	"	"	1/4	100
Fournier, France [109]	*Escherichia coli* (24)	2009–2010	Urinary tract	Agar dilution (≤32 mg/L)	≤1/≤1	99.0
Bouxom, France [51]	*Klebsiella pneumoniae* (50)	2016	Urinary tract, blood	Agar dilution (≤32 mg/L)	8/64	86.0
	Escherichia coli (100)	"	"	"	1/2	98.0
van den Bijllaardt, Netherlands [338]	*Klebsiella pneumoniae* (201)	2016–2017	Urine, blood, respiratory tract	Agar dilution (≤32 mg/L)	16/>128	87.6
	Escherichia coli (775)	"	"	"	1/2	95.9
PEG, Germany [256]	*Klebsiella pneumoniae* (53)	2013	NR	Broth microdilution (≤32 mg/L)	16/64	88.7
	Escherichia coli (89)	"	"	"	2/4	96.6
Walkty, Canada [344]	*Escherichia coli* (162)	2007–2017	Urine	Agar dilution (≤64 mg/L)	2/4	96.9
Zykov, Norway [362]	*Escherichia coli* (105)	2010–2011	Urine, blood	Gradient test (≤32 mg/L)	2/2	100

NR: Not reported.

[a]Susceptibility is defined as a MIC value equal to or lower as the breakpoint concentration.

nosocomial infections. *Klebsiella* spp. predominantly cause nosocomial pneumonia, whereas pathogenic serotypes of *E. coli* may cause gastrointestinal and urinary tract infections.

As shown in Table 10, susceptibility rates of ESBL-producing enterobacteria like *E. coli* or *K. pneumoniae* remain at high levels of 60 to 100% across Europe.

The *in vitro* susceptibility of fosfomycin against carbapenemase-producing Enterobacterales is between 42 and 100% in European and selected non-European countries and there seems to be no tendency towards a decreased activity against these pathogens over time – yet (Table 11).

Table 11: Susceptibility to fosfomycin of extensively drug-resistant (carbapenem-resistant) *Enterobacterales* clinical isolates from Europe and the Americas.

First author, geographic region [Ref.]	Pathogen (no. of isolates)	Years of collection	Source	Method (breakpoint[a])	Fosfomycin $MIC_{50/90}$ (mg/L)	Resistance factors	Susceptibility rate[a] (%)
Kaase, Germany [163]	*Klebsiella pneumoniae* (50)	2009–2011	Urine, lower respiratory tract, wounds	Agar dilution (≤32 mg/L)	16/256	KPC-2, KPC-2 and VIM-1, KPC-3, VIM-4, OXA-48, OXA-162, impermeability	72.0
	Escherichia coli (24)	"	"	"	1/256	KPC-3, VIM-1, OXA-48, impermeability	83.3
	Enterobacter cloacae (17)	"	"	"	16/512	VIM-1, OXA-48	76.5
Souli, Greece [313]	*Klebsiella pneumoniae* (17)	2007–2009	Clinical (inpatients)	Agar dilution (≤32 mg/L)	32/256	KPC-2	76.5
Pena, Spain [258]	*Klebsiella pneumoniae* (79)	2010–2012	Urine, respiratory tract, pus, surgical wounds, blood, CSF, catheter	Agar dilution (≤32 mg/L)	NR	IMP-22, VIM-1, KPC-2, OXA-48	78.5
	Enterobacter spp. (17)	"	"	"	NR	NR	76.5

First author, geographic region [Ref.]	Pathogen (no. of isolates)	Years of collection	Source	Method (breakpoint[a])	Fosfomycin $MIC^{50/90}$ (mg/L)	Resistance factors	Susceptibility rate[a] (%)
Livermore, UK [203]	*Klebsiella pneumoniae* (52)	2008–2010	Clinical	Agar dilution (≤32 mg/L)	32/≥256	IMP, VIM, KPC, OXA-48, impermeability (± ESBL)	48.1
	Escherichia coli (7)	"	"	"	2/4	IMP, NDM, VIM, SME-1, OXA-48, impermeability (± ESBL)	100.0
	Enterobacter spp./ *Citrobacter freundii* (20)	"	"	"	16/64	IMP, NDM, VIM, SME-1, OXA-48, impermeability (± ESBL)	80.0
Perdigão-Neto, Brazil [259]	*Klebsiella pneumoniae* (27)	2010–2013	Urine, blood, respiratory tract	Agar dilution (≤32 mg/L)	16/32	KPC	≥90%
	Enterobacter spp. (10)	"	"	"	64/64	NR	NR
Rizek, Brazil [279]	*Klebsiella pneumoniae* (50)	NR	Clinical	Agar dilution (≤32 mg/L)	16/32	KPC-2	≥90%
	Serratia marcescens (8)	"	"	"	32/32	KPC + intermediate susceptible to tigecycline	100.0
Flamm, USA [103]	*Escherichia coli* (11)	2014–2015	Clinical	Agar dilution (≤64 mg/L)	1/>256	carbapenem-resistant (not further specified)	81.8
	Klebsiella pneumoniae (12)	2015	"	"	8/64	"	91.7
Shortridge, Eastern Europe [305]	*Klebsiella pneumoniae* (36)	2016	Clinical	Agar dilution (≤64 mg/L)	32/128	carbapenem-resistant (not further specified)	80.6

Table 11: Susceptibility to fosfomycin of extensively drug-resistant (carbapenem-resistant) *Enterobacterales* clinical isolates from Europe and the Americas.

First author, geographic region [Ref.]	Pathogen (no. of isolates)	Years of collection	Source	Method (breakpoint[a])	Fosfomycin $MIC_{50/90}$ (mg/L)	Resistance factors	Susceptibility rate[a] (%)
Bielen, Croatia [41]	*Klebsiella pneumoniae* (8)	2014–2016	Clinical	Agar dilution (≤64 mg/L)	128/512	VIM-1, SHV-1, CTX-M-15, TEM-1, NDM-1, OXA-48	42
	Citrobacter freundii (17)	"	"	"	4/16	VIM-1, CTX-M-15, TEM-1, CMY-2/4	96
	Enterobacter spp. (28)	"	"	"	16/128	VIM-1, SHV-1, CTX-M-15, TEM-1, NDM-1, OXA-48, DHA, CMY-4	86

NR: Not reported.

[a]Susceptibility is defined as a MIC value equal to or lower as the breakpoint concentration.

Fosfomycin is active against pathogens expressing β-lactamases irrespective of Ambler class (Table 12).

In further studies, Maraki *et al.* evaluated the *in vitro* activity of fosfomycin against a total of 578 urinary isolates collected in Greece. The collection included ESBL-producing *E. coli* and *K. pneumoniae* (total 29 strains) isolated from the urinary tract, which were all found to be susceptible to fosfomycin (Maraki *et al.* [209]). Furthermore, the authors reported 12 strains of colistin-resistant *K. pneumoniae* and 25 strains of carbapenem-resistant *K. pneumoniae*, of which 58% and 60%, respectively, were susceptible to fosfomycin (Maraki *et al.* [209]). The most recent longitudinal data from the German Paul-Ehrlich-Society for Chemotherapy indicate a continuously high susceptibility of important problem bacteria such as carbapenemase-producing *K. pneumoniae* and ESBL-producing *E. coli* and *K. pneumoniae* towards i. v. fosfomycin (see also Table 10 and Table 11). Data from a recent review conducted by Vardakas *et al.* demonstrated susceptibilities of ESBL-producing *Escherichia coli* ranging from 81% to 100% (95.1%, 94.3–95.9%), of ESBL-producing *Klebsiella pneumoniae* from 15% to 100% (83.8%, 78.7–89.4%) and of carbapenem-resistant (CR) *K. pneumoniae* from 39.2% to 100% (73.5%, 66.4–81.4%) (Vardakas *et al.* [341]).

A systematic review by Falagas *et al.* covered further studies of the susceptibilities of multidrug-resistant, including ESBL-producing, enterobacteria to fosfomycin and reported consistently high susceptibility rates of up to 99% (Falagas *et al.* [98]).

Overall, fosfomycin can be seen as one of only few therapeutic options for the treat-

Table 12: Bactericidal activity of fosfomycin against pathogens expressing β-lactamases (see also Tables 10 and 11).

Ambler class	β-Lactamases	Resistance factors	Fosfomycin activity
A	Penicillinases	TEM, SHV, CTX-M (ESBL), KPC-Carbapenemases	Yes
B	Metallo-β-lactamases	NDM, VIM, IMP	Yes
C	Cephalosporinases	AmpC	Yes
D	Oxacillinases	OXA-48	Yes

ment of infections due to multidrug-resistant *Enterobacterales* independent of the type of β-lactamases.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a ubiquitous gram-negative organism occurring particularly in moist environments. *P. aeruginosa* is considered one of the most important pathogens in hospitals, especially in the intensive care setting, due to its associations with respiratory equipment, sinks, and hand basins. Immunocompromised hosts are particularly at risk of severe infections and this species is one of the leading organisms responsible for ventilator-associated pneumonias. *P. aeruginosa* infections can cause high morbidity and mortality among immunocompromised patients, multidrug-resistant strains producing an even higher fatality rate (Meradji *et al.* [220]). The antimicrobial activity of fosfomycin against a randomly selected sample of 30 multidrug-resistant, ESBL-producing clinical isolates of *P. aeruginosa* was studied, and MIC values covered a wide range – from 4 to 512 mg/L (Falagas *et al.* [95]). Maraki *et al.* described 9 strains of carbapenem-resistant *P. aeruginosa*, of which 89% were sensitive to fosfomycin (disk diffusion method) (Maraki *et al.* [209]). More recent data from the Paul-Ehrlich-Society for Chemotherapy indicate that 76% of *P. aeruginosa* strains (557/733) retained sensitivity to fosfomycin in terms of an MIC of 128 mg/L (PEG [256]). Furthermore, recent data from more than 1 400 gram-negative and 800 gram-positive clinical isolates collected during the SENTRY Antimicrobial Surveillance programme in US medical centres showed that fosfomycin had high levels of activity against 95% of the 100 *P. aeruginosa* isolates tested, with MIC ≤ 128 µg/mL using an agar dilution technique (Flamm *et al.* [103]). Cai *et al.* found that fosfomycin combined with certain aminoglycosides showed positive effects against *P. aeruginosa in vitro*, as well as in a rat biofilm infection model (Cai *et al.* [57]). In this context, the combination of gentamycin plus fosfomycin showed synergy against *P. aeruginosa* biofilms (Wang *et al.* [345]). In highly resistant *P. aeruginosa* strains, combination therapy of fosfomycin with ceftazidime/avibactam or meropenem significantly enhances the antimicrobial activity by enhancing bactericidity and reducing the emergence of resistances compared to the individual drugs (Papp-Wallace *et al.* [254], Drusano *et al.* [87], Albiero *et al.* [6]).

2.4.2.3 Activity on biofilms

Microorganisms irreversibly attach to surfaces by producing an extracellular polysaccharide matrix, giving rise to microbial biofilms. As bacteria in biofilms are in a reduced metabolic state and the biopolymer mass around the bacteria builds a solid diffusion barrier, antibiotic concentrations up to 1 000 times higher compared to planktonic cultures may be necessary for bacterial killing. Biofilm-associated infections are therefore considered difficult-to-treat and pose a significant threat to public health. The presence of biofilms not only challenges the treatment in catheter- and implant-related infections, but also in chronic osteomyelitis,

endocarditis, chronic recurrent urinary tract infections, chronic wound infections, and bronchopulmonary infections (Ceri *et al.* [60], Bandeira *et al.* [24], Donlan [83]).

Fosfomycin has the ability to penetrate into biofilms (Marchese *et al.* [210], Kumon *et al.* [186], Kono *et al.* [182], Ruiz *et al.* [287]). There is considerable evidence from both *in vitro* and *in vivo* biofilm infection models indicating that fosfomycin, alone or in combination with other antibiotics, offers excellent efficacy in reducing or eradicating biofilm-embedded bacteria. Furthermore, previous studies revealed that fosfomycin can also modify biofilm structure and even prevent biofilm formation (Falagas *et al.* [98], Mikuniya *et al.* [224, 225], Ruiz *et al.* [287]).

Fosfomycin was found one of the most effective drugs against *in vitro* biofilms formed by *S. aureus* (Amorena *et al.* [13], Tang *et al.* [320, 321]). In MRSA biofilms, combinations with fosfomycin showed higher activity than those with rifampicin and, in contrast, did not induce resistance (Tang *et al.* [321]). A significant reduction of *Staphylococcus epidermidis* biofilm density could be observed in the presence of fosfomycin (Presterl *et al.* [269], Hajdu *et al.* [139]).

Enterococci are considered as difficult-to-treat pathogens, especially when located in biofilms. Fosfomycin-based combinations have been described to synergistically enhance anti-enterococcal effects *in vitro* (Tang *et al.* [322], Descourouez [79], Zheng *et al.* [359]). In the case of adherent linezolid-resistant isolates of *Enterococcus faecalis*, daptomycin combined with fosfomycin demonstrated a significantly better activity than daptomycin or fosfomycin alone and effectively killed the adherent cells in mature biofilms (Zheng *et al.* [359]).

Fosfomycin was furthermore among the most efficient drugs at penetrating biofilms of gram-negative species grown on siliconised latex urinary catheters (Rodríguez-Martinez *et al.* [280]). Visualised using a variety of microscopy techniques, fosfomycin induced functional changes in the outer membrane structure of *P. aeruginosa* growing in biofilms, thereby increasing its permeability for other drugs such as fluorchinolones (Kumon *et al.* [186], Monden *et al.* [228]). In experimental biofilms of *E. coli*, the addition of fosfomycin to gentamicin was highly favourable (Wang *et al.* [345]). Breakdown of initial and mature *E. coli* biofilms was reported to be increased by *N*-acetylcysteine, a known mucolytic agent (Marchese *et al.* [210]). Fosfomycin even showed good inhibitory effects *in vitro* on biofilms formed by MDR species including β-lactamase-producing *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., and *Pseudomonas aeruginosa* (Gopichand *et al.* [122]).

In addition, data from in vivo biofilm infection models support the importance of fosfomycin. Using the validated guinea pig model of the Trampuz group, the highest cure rate of 83% against MRSA biofilms has been achieved for the combination of fosfomycin with rifampicin (Mihailescu *et al.* [222]). In comparison, the combination of daptomycin and rifampicin cured biofilm infections in only 67%, whereas all single drugs (fosfomycin, daptomycin, and tigecycline) as well as rifampicin-free fosfomycin combinations showed no cure of MRSA implant infections (Figure 14). Further evidence for combination therapy in MRSA biofilm-related infections were published by the groups of Shi, Morikawa and Lingscheid. They reported high levels of efficacy of fosfomycin in combination with vancomycin (Shi *et al.* [303]), daptomycin (Lingscheid *et al.* [202]), or aminoglycosides (Morikawa *et al.* [230]). In an experimental rat model of chronic implant-associated MRSA osteomyelitis, treatment with fosfomycin was shown to be superior to daptomycin or vancomycin, respectively, with no emergence of resistance (Lingscheid *et al.* [202], Poeppl *et al.* [266]).

Interestingly, fosfomycin as a single agent eradicated biofilm bacteria from 42% of cages in the appropriate foreign-body infection model of *Enterococcus faecalis*, whereas rifampicin

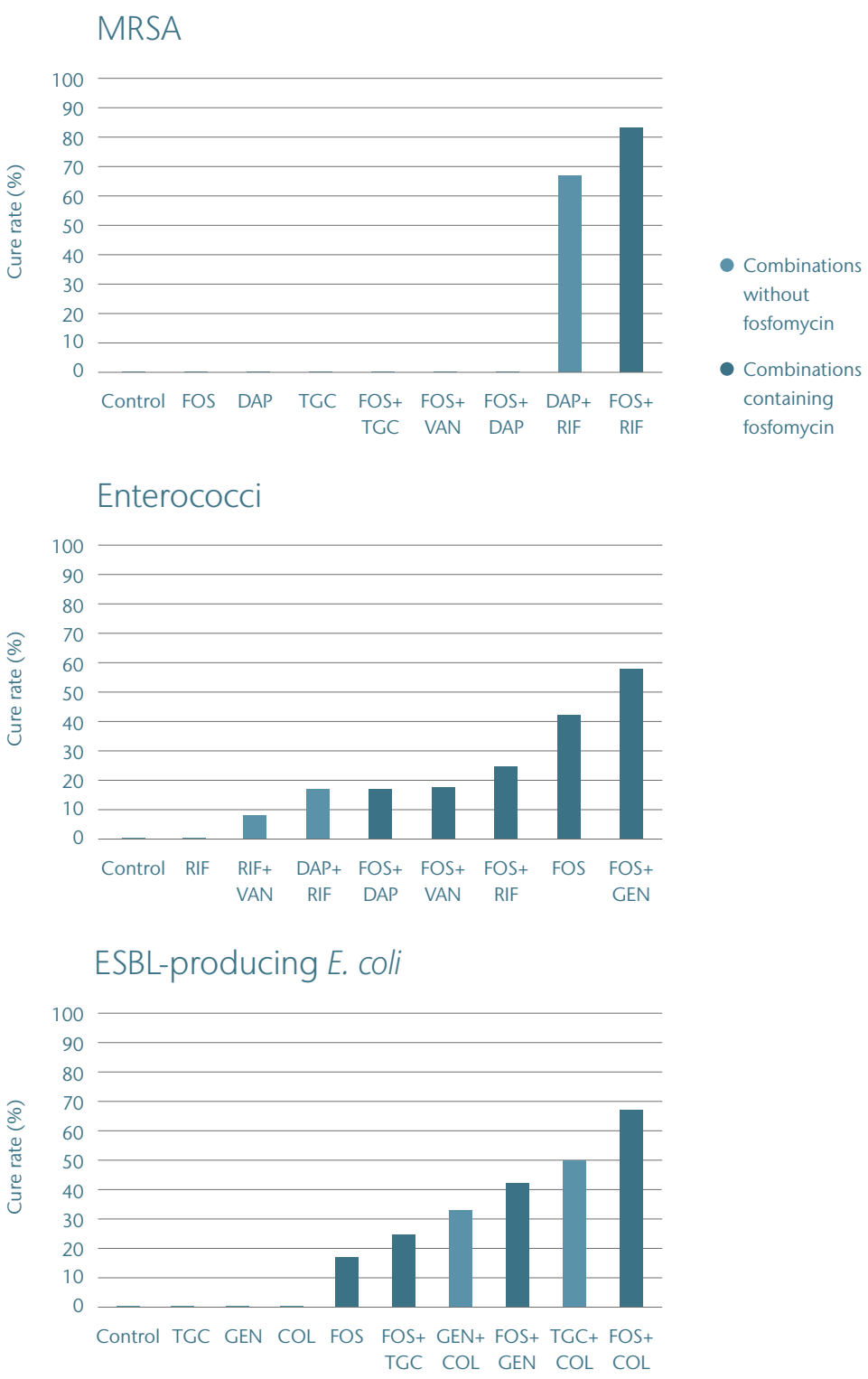


Figure 14: Summary of the activities of various antibiotics and combinations of antibiotics against different bacteria in biofilms in in vivo guinea pig infection models. (Corvec et al. [69], Oliva et al. [252], Mihailescu et al. [222]). FOS: fosfomycin; GEN: gentamicin; TGC: tigecycline; COL: colistin; RIF: rifampicin; DAP: daptomycin; VAN: vancomycin.

did not show any activity. In combination with gentamicin, which was by far the most effective combination, fosfomycin cleared 77% and cured 58% of cages. No emergence of fosfomycin resistance was observed in vivo (Oliva *et al.* [252], Figure 14).

Corvec *et al.* found fosfomycin to be superior to other antibiotics, as it was the only single agent able to eradicate ESBL-positive biofilm-producing *Escherichia coli* in the guinea pig model. In terms of the cure rate of biofilm-associated infections, the combination of fosfomycin with colistin was most effective (67%) and significantly better than fosfomycin alone (Corvec *et al.* [69], Figure 14).

Likewise, Cai *et al.* demonstrated that the use of fosfomycin in combination with aminoglycosides was effective against *Pseudomonas aeruginosa* in a rat model of biofilm-associated infections (Cai *et al.* [57]). The combination of fluorchinolones and fosfomycin resulted in destruction and disappearance of *P. aeruginosa* multilayer biofilms from the surfaces of polyethylene tubes in a urinary tract infection rat model, as detected by scanning electron microscopy (Mikuniya *et al.* [224]).

Modification of biofilm structure by fosfomycin has also been described by other groups (Shi *et al.* [303], Presterl *et al.* [269], Hajdu *et al.* [139], DiCicco *et al.* [81]). It has been suggested that fosfomycin reaches the biofilm-embedded bacteria first, and rapidly kills or weakens them, which in turn leads to a reduced production of biofilm matrix, a decrease in film thickness, and a decrease in the adhesion of bacteria to surfaces. Thereby, fosfomycin functions as a "door opener" for the second antimicrobial agent, which then can better reach the bacteria and accomplish the desired antimicrobial effect (DiCicco *et al.* [81]). Kusachi and colleagues provided clinical evidence for this hypothesis (Kusachi *et al.* [188], Section 3.8).

In addition, fosfomycin also helps to prevent biofilm formation. Marquès *et al.* found fosfomycin to be effective in inhibiting *Staphylococcus aureus* biofilm formation at concentrations near the breakpoint (Marquès *et al.* [212]). In a number of studies, fosfomycin showed good activity on biofilm producing strains of typical urinary tract pathogens including *E. coli*, *K. pneumoniae*, and *Pseudomonas aeruginosa*, with decreases in biofilm formation up to 84% (Gopichand *et al.* [122], Marchese *et al.* [210], Cai *et al.* [57], Ruiz *et al.* [287]). Moreover, fosfomycin reduces the adhesion of enterobacteria to urinary tract epithelia (Karageorgopoulos *et al.* [169], Marchese *et al.* [210]).

In conclusion, there is plenty of evidence showing that fosfomycin is an excellent choice for the combination therapy of biofilm-associated infections.

2.4.2.4 Synergism/antagonism

Fosfomycin inhibits an early stage in bacterial cell wall synthesis, which explains its synergistic effects with other later-stage cell wall synthesis-inhibiting antibiotics (such as β-lactams or glycopeptides). Moreover, fosfomycin increases bacterial cell wall permeability, thereby facilitating the effects of other antimicrobial substances. *In vitro* tests have shown that combinations of fosfomycin with β-lactam antibiotics such as penicillins (e. g., ampicillin), cefazolin, or carbapenems produce effects which are mostly additive or synergistic. Combinations of fosfomycin with carbapenems displayed high synergistic potential, especially for the treatment of multidrug-resistant pathogens. Combinations with carbapenems, colistin, and tigecycline showed *in vitro* synergy against ESBL *K. pneumoniae* and CR *K. pneumoniae*, as well as CR *P. aeruginosa* (Avery *et al.* [21], Avery *et al.* [22], Papp-Wallace *et al.* [254], Mikhail *et al.* [223], Samonis *et al.* [289], Santos *et al.* [290]).The same holds true for combinations of fosfomycin with most agents used for the treatment of infections caused by staphylococci (linezolid, daptomycin, vancomycin). In daily clinical practice, fosfomycin has been successfully combined with most common antibiotics, including

β-lactams, aminoglycosides, glycopeptides, polymyxins, lincosamides and rifamycins (Falagas *et al.* [98]). The combination of fosfomycin with ampicillin and cefotaxime resulted in synergistic effects against many *Proteus vulgaris*, Enterobacter and Providencia rettgeri strains (Chin *et al.* [62]).

The mechanism of action of fosfomycin, which interferes with the early steps in bacterial cell wall formation, leads to the expectation of additive or synergistic actions when combined with other antibiotics with different targets. Synergy rates of 36% to 74% are observed, depending on species. Fosfomycin must clearly be regarded as a potent combination partner, given that virtually no antagonism has been reported for any combination tested (Kastoris *et al.* [173], Falagas *et al.* [98]). Table 13 presents an incomplete list of the most important reported interactions of fosfomycin with other antibiotic substances.

Table 13: *In-vitro* effects of fosfomycin used in combination with other antibiotic substances against various bacteria.

Antibiotic	Organism	Effect	Reference
Amikacin	*P. aeruginosa*	S-I	[88], [144], [346]
Amikacin	CR *P. aeruginosa*	S	[57]
Cefazolin	MSSA, MRSA	S	[129]
Cefepime	*P. aeruginosa*	S	[250]
Cefotaxime	MRSA	S	[268], [336]
Ceftazidime	*P. aeruginosa*	S-I	[88], [250], [325]
Ceftazidime/avibactam	MDR *P. aeruginosa*	S	[22], [254]
Ceftazidime/avibactam	CR *K. pneumoniae*	S	[223]
Ceftolozane/tazobactam	CR *P. aeruginosa*	S	[22], [241]
Ciprofloxacin	Coag.-neg. S.	S	[140]
Ciprofloxacin	MSSA/MRSA	S	[140], [335]
Ciprofloxacin	*P. aeruginosa*	S	[144], [355]
Ciprofloxacin	*Enterococcus* spp.	S	[140]
Colistin	CR *A. baumannii*	S-I	[190]
Colistin	ESBL *E. coli*	S	[69]
Colistin	KPC	S	[289]
Colistin	CR *P. aeruginosa*	S	[80]
Daptomycin	*Enterococcus* spp.	S	[276]
Daptomycin	MRSA	S	[4], [202], [222]
Daptomycin	VRE	S	[79]
Gentamicin	*E. coli*	S	[251]
Gentamicin	ESBL *E. coli*	S	[251]
Gentamicin	*K. pneumoniae*	S	[251]
Gentamicin	MSSA/MRSA	S-I-A	[11], [251]
Gentamicin	*P. aeruginosa*	S-I	[250], [251]

Table 13: *In-vitro* effects of fosfomycin used in combination with other antibiotic substances against various bacteria.

Antibiotic	Organism	Effect	Reference
Gentamicin	CR *P. aeruginosa*	S	[57]
Imipenem	Coag.-neg. S.	S	[74]
Imipenem	*Enterococcus* spp.	S	[74]
Imipenem	ESBL *E. coli*	S	[289]
Imipenem	ESBL *K. pneumoniae*	S	[289]
Imipenem	KPC	S	[289]
Imipenem	MDR *P. aeruginosa*	S	[289]
Imipenem	MSSA/MRSA	S	[235]
Imipenem	*P. aeruginosa*	S-I	[250], [270], [325]
Imipenem	CR *P. aeruginosa*	S	[187]
Levofloxacin	*P. aeruginosa*	S-I	[224], [250]
Linezolid	MSSA/MRSA	S	[286], [288], [355]
Linezolid	VRE	S	[79], [322]
Linezolid	*S. epidermidis*	S	[129]
Meropenem	ESBL *E. coli*	S	[289]
Meropenem	ESBL *K. pneumoniae*	S	[289]
Meropenem	KPC	S	[289]
Meropenem	*P. aeruginosa*	S	[250]
Meropenem	MDR *P. aeruginosa*	S	[289]
Meropenem	CR *P. aeruginosa*	S	[187]
Meropenem	MSSA	S	[129]
Oxacillin	MRSA, MRSE	S	[101]
Penicillin	MSSA	S	[48]
Piperacillin/tazobactam	*P. aeruginosa*	S	[242]
Rifampicin	Coag.-neg. S.	S	[140]
Rifampicin	*Enterococcus* spp.	S	[308]
Rifampicin	MSSA/MRSA	S-A	[140], [222]
Rifampicin	VRE	S	[322]
Rifampicin	*S. epidermidis*	S	[129]
Teicoplanin	VRE	S	[322]
Temocillin	CR *E. coli*	S	[39]
Tigecycline	*Enterococcus* spp.	S	[308]
Tigecycline	ESBL *E. coli*	S	[69], [289]

Antibiotic	Organism	Effect	Reference
Tigecycline	ESBL *K. pneumoniae*	S	[289]
Tigecycline	KPC	S	[289]
Tigecycline	VRE	S	[322]
Tobramycin	CR *P. aeruginosa*	S	[57]
Vancomycin	Coag.-neg. S.	I	[116]
Vancomycin	MSSA/MRSA	S-I	[129], [222], [235]
Vancomycin	VRE	S	[322]
Vancomycin	*S. epidermidis*	S	[129]

S: Synergistic; I: Indifferent; A: Antagonistic; CR: Carbapenem-resistant; Coag.-neg. S.: Coagulase-negative staphylococci; ESBL: Extended-spectrum β-lactamases; KPC: *Klebsiella pneumoniae* carbapenemase; MDR: Multidrug-resistant; MRSA: Methicillin-resistant *S. aureus*; MSSA: Methicillin-sensitive *S. aureus*; VRE: Vancomycin-resistant enterococci.

2.4.2.5 Nephroprotection

A nephroprotective effect has been described for fosfomycin when co-administered with nephrotoxic agents. Early studies on the mechanism of this action reported by Inouye *et al.* indicated that the nephroprotective effect of fosfomycin is mediated by stabilisation of lysosomal membrane integrity in kidney cells (*in-vitro* studies) and suppression of myeloid body formation (*in vivo*, Inouye *et al.* [154]). The authors expanded their investigations by using fosfomycin analogues and demonstrated that both the phosphonic-acid and the epoxide functions were necessary for the nephroprotective effect (Inouye *et al.* [154]). They also noted that any interpretation of the protective effect of fosfomycin may have to take into account the mode of action of the specific nephrotoxic agent used. The nephrotoxic effect of aminoglycosides, for example, is mediated by increases in the lability of the lysosomal membranes of proximal tubule cells as a result of interference with phospholipid catabolism (Inouye *et al.* [154]). In this case, the nephroprotective mechanism of fosfomycin provides good neutralisation of this particular effect. More recent studies have demonstrated that fosfomycin can also counter gentamicin-induced lipid peroxidation in rat renal cortex mitochondria, thereby providing an additional nephroprotective mechanism (Yanagida *et al.* [356]).

The protective effects of fosfomycin were further confirmed in animal studies investigating its activity against vancomycin- and cisplatin-induced nephrotoxicity (Nakamura *et al.* [233]). Dose-dependent increases in plasma creatinine and urea nitrogen produced by both compounds were significantly reduced in magnitude by fosfomycin. The authors concluded that nephroprotection provides new therapeutic opportunities regarding the clinical use of vancomycin in renal failure.

Clinically, Bär *et al.* reported a small series of cases (5 patients) where elevated serum creatinine concentrations (175 ± 41 µg/L) regressed towards lower values (84 ± 44 µg/L) when fosfomycin was administered in addition to vancomycin (Bär *et al.* [27]). Hoyer *et al.* treated recipients of renal allografts with fosfomycin or saline (controls) in an open randomised clinical trial and observed statistically significant improvements in overall survival and graft function after 10 years of follow-up in the fosfomycin-treated group over the control group (Hoyer *et al.* [152]). Sirijatuphat *et al.* studied the efficacy and safety of fosfomycin plus colistin combination therapy vs colistin monotherapy in a randomised controlled trial in patients with *Acinetobacter baumannii* infections (n = 47 patients per group). Although no statistically significant differences in colistin nephrotoxicity were observed, there was a trend towards a lower incidence of

acute renal failure in the fosfomycin combination subgroup, excluding patients who received concurrent carbapenems in both groups (37.2% vs 48.7%, $p = 0.37$), which is noteworthy given the limited statistical power of this preliminary trial (Sirijatuphat *et al.* [310]).

First endeavours to investigate the underlying mechanism of the renoprotective effect of fosfomycin in patients were performed by Al-Aloul *et al.* They postulated that fosfomycin competes with aminoglycosides at renal binding sites and may therefore afford a renoprotective effect when used in combination therapy. For this purpose, a prospective randomised crossover trial in patients suffering from cystic fibrosis was performed. At an acute pulmonary exacerbation, 18 adult CF patients received either 14 days of i. v. tobramycin or i. v. tobramycin and i. v. fosfomycin, both in combination with a second i. v. antibiotic (colistin). The renoprotective activity was explored by using markers of acute renal tubular damage (*N*-acetyl-β-D-glucose-aminidase (NAG), alanine amino-peptidase (AAP) and β_2-microglobulin). Urinary NAG and AAP following treatment with concomitant fosfomycin were significantly lower after 14 days of treatment than those after treatment with tobramycin and colistin alone. Fosfomycin attenuated the total 24 h urinary protein leak. Thus, the addition of fosfomycin reduces acute renal injury caused by i. v. aminoglycoside therapy in CF pulmonary exacerbations (Al-Aloul *et al.* [5]).

Consideration should be given to fosfomycin-induced nephroprotection, particularly in situations where nephrotoxic combination partners such as aminoglycosides or polymyxins are indicated.

2.4.2.6 Mode of resistance

Although introduced into clinical practice more than four decades ago and used for a broad range of indications, most microbiological surveillance studies have not shown any significant loss of the antimicrobial activity of fosfomycin against pathogens over time (Karageorgopoulos *et al.* [168]). While some emergence of resistances is seen *in vitro*, as for many other antibiotics, this seems to be less of an issue with gram-positives, particularly *S. aureus*, than with gram-negative species (Noel *et al.* [244]). Resistance against fosfomycin can generally be traced back to different resistance mechanisms:

- Changes in the transport system across the bacterial cell wall.
- Alteration of the target (*MurA*).
- Inactivation of the antibiotic (enzyme-mediated cleavage of the epoxide or detoxification of fosfomycin).

Changes in the transport system across the bacterial cell wall

Changes in the transport of fosfomycin across the bacterial cell wall decrease permeability to fosfomycin. Impaired fosfomycin transport has been established as the main mechanism of acquired resistance against fosfomycin. Chromosomal mutations in any of the structural genes mediating fosfomycin uptake, i. e., the glycerol-3-phosphate transporter (*GlpT*) or the glucose-6-phosphate transporter (*UhpT*), can thus result in fosfomycin resistance.

Alteration of the target (MurA)

Modification of the enzyme targeted by fosfomycin (*MurA*), particularly point mutations in the binding site, have been shown to mediate resistance to fosfomycin. However, the impact of these types of mutations on acquired resistance seems to be rather low. *MurA* modification is the resistance mechanism in naturally resistant species, such as *M. tuberculosis* and *B. burgdorferi* (Castañeda-Garcia *et al.* [59]).

Inactivation of the antibiotic

Enzyme systems capable of detoxifying fosfomycin, either by enzymatic cleavage of the epoxide ring or phosphorylation of the phosphonate group, have been described in the literature (Figure 15). The metalloenzymes *FosA*, *FosB*, and *FosX* cleave the epoxide structure using glutathione (*FosA*), bacillithiol and other thiols (*FosB*), or water (*FosX*) as nucleophiles. Kinases such as *FomA* and *FomB* catalyse phosphorylation of fosfomycin to the di- or triphosphate, respectively (Castañeda-Garcia *et al.* [59], Silver [307]). Although *FosA* is also encoded in the genomes of some gram-negative species, recent data show that the presence of *FosA* does not appear to correlate with susceptibility to fosfomycin (White *et al.* [349]). *Fos* gene mediated resistance was not found to appear more frequently in ESBL-producing *E. coli* (Walkty *et al.* [344]).

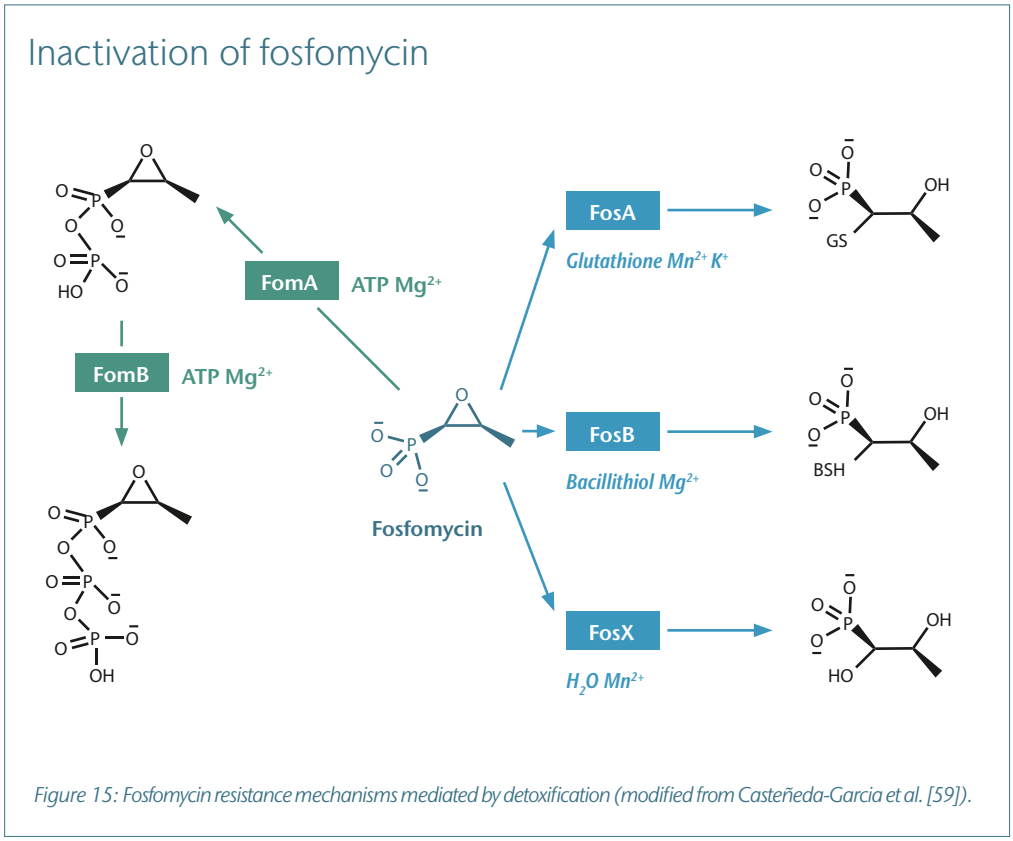


Figure 15: Fosfomycin resistance mechanisms mediated by detoxification (modified from Casteñeda-Garcia et al. [59]).

Clinical impact

The number of resistant mutants developing or persisting in daily clinical routine remains low. In clinical isolates, permeability-mediated resistance due to mutation of the uptake transporter is the main mechanism of resistance. These isolates are resistant to fosfomycin *in vitro*. However, mutant strains lose their ability to grow on multiple carbohydrate sources. This acquired fosfomycin resistance therefore comes with a detriment regarding evolutional fitness and a reduced virulence (Castañeda-Garcia *et al.* [59], Lucas *et al.* [206]). Further studies have shown that other mechanisms, such as modifications of *MurA*, are extremely rare because of the central role of this enzyme in peptidoglycan synthesis. *MurA* mutation frequencies are typically three orders of magnitude lower than mutations in genes inactivating fosfomycin transport, which limits this mechanism to naturally resistant species (Castañeda-Garcia *et al.* [59]). Further studies on plasmid-mediated resistance mechanisms (FosA and FosB) pointed to a very low prevalence among enterobacteria and no transfer mechanism was found in a population of *P. aeruginosa* strains (Arca *et al.* [18]). However,

data reported from parts of East Asia (China, South Korea and Japan) since 2006 have demonstrated fosfomycin-modifying genes located on transposons and conjugative plasmids from human clinical strains, resulting in fosfomycin resistance (Ho *et al.* [150], Lee *et al.* [189], Wachino *et al.* [342]).

Overall, it can be concluded that fosfomycin resistance currently occurs mainly during *in vitro* testing and may have a low level of relevance in typical clinical settings. This finding is in line with persistently low resistance rates despite the long history of fosfomycin therapy (Grabein *et al.* [126]). In addition, recent data from a large randomised control trial as well as from daily clinical practise do not indicate any emergence of fosfomycin resistance during therapy (Kaye *et al.* [175], Putensen *et al.* [272]). A further measure which should help prevent the development of resistance consists of combining fosfomycin with other antibiotics. The choice of combination partner should be based on antimicrobial activity against the pathogen causing the infection as well as potential synergy.

2.4.3 Susceptibility/resistance testing

- Agar dilution is the standard method for fosfomycin susceptibility testing.
- Alternative methods are disk-diffusion, gradient test, and automated methods.

For an effective planning of anti-infective treatment, in particular for the de-escalation towards targeted therapy after initial empiric treatment, it is important to determine the susceptibility of pathogens towards antibiotics as rapidly as possible. Susceptibility testing of isolates has become a major predictive marker for the success of antibiotic therapy, though a large variety of different test methods are available.

Manual methods

One of the oldest methods for determining antimicrobial susceptibility is the *agar dilution test (AD)*, in which bacteria are grown on agar containing serial dilutions of antibiotics. The test provides quantitative results, including a minimum inhibitory concentration (MIC) for the respective pathogen, and is currently regarded as the gold standard for fosfomycin susceptibility testing because of its accuracy and good correlation between *in-vitro* and *in-vivo* results (Haag *et al.* [133]). Nowadays, novel easy-to-use agar dilution methods are commercially available to facilitate the labour- and time-intensive standard technique.

Another similar assay for determining MIC values is the *broth dilution test (BD)*, in which antibiotic dilutions are made in broth medium instead of agar. However, discordant results have been reported when determining bactericidal endpoints with broth dilution (the so-called skip-tube phenomenon). MIC values should therefore only be estimated using agar dilution or gradient tests.

In contrast to serial dilutions, *disk diffusion tests (DD)* provide a qualitative indication based on zone diameters. Growth inhibition zone diameters provide a semi-quantitative indication of susceptibility (Jorgensen *et al.* [159]). The g*radient diffusion test (GD)* (commercialised as the E-test or MIC test strips), in which a plastic/paper strip is impregnated with a gradient of an antimicrobial agent, is a modified version of the disk diffusion test. Growth inhibition zones in the gradient test are elliptical and give an estimate of the MIC.

Regardless of the test system used, it is important to note that all *in-vitro* susceptibility test methods for fosfomycin require the addition of glucose-6-phosphate (G-6-P) to either the medium, the disk or the gradient strip (25 mg/L of glucose-6-phosphate: AD, BD, GD; 50 µg of glucose-6-phosphate: DD) Most commercially available systems implement these EUCAST or Clinical and Laboratory Standards Institute (CLSI) recommendations, so no further addition of G-6-P is required. However, it is always important to check the product manual.

Automated systems

Several automated systems have been developed and commercialised with the aims of increasing antimicrobial sensitivity testing throughput and decreasing the time to test readout. Automated systems rely on parallel identification and continuous measurement of the growth of the isolated organism during the test. These systems identify test strains by comparing their growth curves with standard curves stored in a database. For fosfomycin susceptibility testing a variety of test cards for both gram-negative and gram-positive species are commercially available depending on the system, but may vary from country to country.

Inhibition zone diameter for disk diffusion and clinical breakpoints

For *E. coli*, zone diameter breakpoints of 24 mm and for wild-type *P. aeruginosa* isolates, an epidemiological MIC cut-off (ECOFF) of 128 mg/L and a corresponding zone diameter of 12 mm have been defined by the EUCAST. In determining the correct zone diameter, isolated colonies within the inhibition zone should be ignored for both *E. coli* and *P. aeruginosa* (for the correct interpretation of zone diameter see www.eucast.org).

For intravenous fosfomycin, the clinical breakpoints established by EUCAST are shown in Table 14 (EUCAST breakpoint table version 10.0, 2020).

Table 14: EUCAST clinical breakpoints for fosfomycin.

Species	Susceptible	Resistant
Enterobacterales	≤32 mg/L	>32 mg/L
Staphylococcus spp.	≤32 mg/L	>32 mg/L

Breakpoints for *E. coli* and *E. faecalis* defined by CLSI apply for oral fosfomycin and urinary tract infections only and cannot be transferred one-to-one to the i. v. form and systemic infections. CLSI breakpoints for i. v. fosfomycin are expected when the i. v. form becomes licensed in the US.

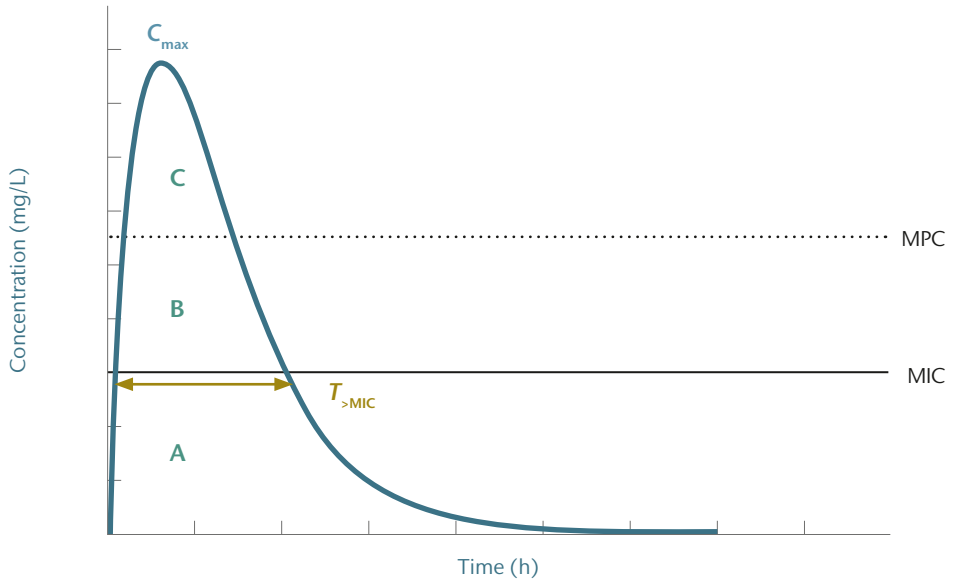
2.4.4 PK-PD indices

- The antibacterial activity of fosfomycin depends on time and concentration.
- Pharmacodynamic targets are available for clinically relevant gram-positives and gram-negatives.

The prediction of clinical and antimicrobial treatment success is essential. The use of a variety of pharmacokinetic-pharmacodynamic (PK-PD) indices to predict the likely clinical success of a given antibiotic regimen continues to increase (Barbour *et al.* [28], Craig, [70]). PK-PD indices are highly predictive of *in-vitro* bacterial eradication and represent valuable determinants of microbial and clinical efficacy in animals and humans

Currently employed PK-PD parameters include the ratio of the unbound peak plasma concentration of the antibiotic to the minimum inhibitory concentration (C_{max}/MIC), the ratio of the 24-hour area under the concentration vs. time curve to the MIC ($AUC_{0–24}$/MIC), or the duration of time when the unbound plasma drug concentration exceeds the MIC (time above MIC, $T_{>MIC}$) (Figure 16). The latter is commonly expressed as the percentage of the dosing interval (%$T_{>MIC}$). These PK-PD indices have only been established for the plasma compartment, though data on antibiotic tissue distributions and concentrations are increasingly utilised in selecting appropriate antimicrobial strategies.

Illustration of PK-PD parameters



C_{max} Concentration dependence (C_{max}/MIC), i.e. aminoglycosides, quinolones

AUC=A+B+C Concentration and time dependence (AUC/MIC), i.e. aminoclycosides, glycopeptides

T Time dependence ($T_{>MIC}$), i.e. beta-lactams

Figure 16: Plot illustrating PK-PD parameters. MIC: Minimum inhibitory concentration, MPC: mutant prevention concentration. Placing antibiotic concentrations inside the MIC/MPC window (area B) is expected to enrich mutant subpopulations (modified from Abdul-Aziz et al. [1]).

Currently available experimental data indicate that both time- (%$T_{>MIC}$) and concentration- ($AUC_{0–24}$/MIC) dependent killing behaviour may be useful PK-PD indices for the prediction of the antimicrobial effect of fosfomycin in tissues and plasma (Pfausler *et al.* [262], Fransen *et al.* [110], VanScoy *et al.* [340], Lepak *et al.* [193], Noel *et al.* [244]). Similar results are also known for other antibiotics that are correlated with more than one dominant PK-PD index, such as aminoglycosides, linezolid, quinolones, or daptomycin (Abdul-Aziz *et al.* [1]). Pharmacodynamic targets of clinically relevant gram-negative and gram-positive pathogens to quantify the magnitude of exposure required for a bactericidal effect (1-log reduction) are 70–100 %$T_{>MIC}$ and 43–83 for the ratio of the 24-hour area under the concentration vs. time curve to the MIC ($AUC_{0–24}$/MIC). Pharmacodynamic targets for *S. aureus* were lower than for *Enterbacterales* (Lepak *et al.* [193], Noel *et al.* [244]).

Within the scope of the recently finalised European referral procedure on fosfomycin in 2020, results from translational modelling have shown that PD targets for a bactericidal activity against both *S. aureus* as well as *Enterobacterales* are well met with daily fosfomycin dosages of 12–24 g/d. This assessment was performed according to regulatory requirements under assumption of both time and concentration dependence and a EUCAST breakpoint of 32 mg/L. As time is a major variable for both PD indices, the scientific committee of the EMA proposed that fosfomycin most likely acts in a time-dependent manner and dosages in the range 12–24 g/d were endorsed for all indications except bacterial meningitis, where higher doses of 16–24 g/d are required (European Medicines Agency [92]; see also Section 2.4.5).

2.4.5 Dosing and administration of fosfomycin

- Fosfomycin has a broad therapeutic margin.
- The recommended daily dosage is 12–24 g (for bacterial meningitis: 16–24 g).
- Dosage recommendations are also available for paediatric population, patients with renal impairment, and those undergoing renal replacement.

Dosing schemes for fosfomycin have been established on the basis of its pharmacokinetic and pharmacodynamic properties and depend on the indication, severity, and site of infection as well as on the susceptibility of the pathogens towards fosfomycin and the estimated creatinine clearance of the patients undergoing treatment. Detailed dosing schemes and tables can be found in the Summary of Product Characteristics at the end of this monograph and in Table 15.

Table 15: General dosage guidelines for adults and adolescents ≥12 years of age (>40 kg) and with an estimated creatinine clearance >80 mL/min.

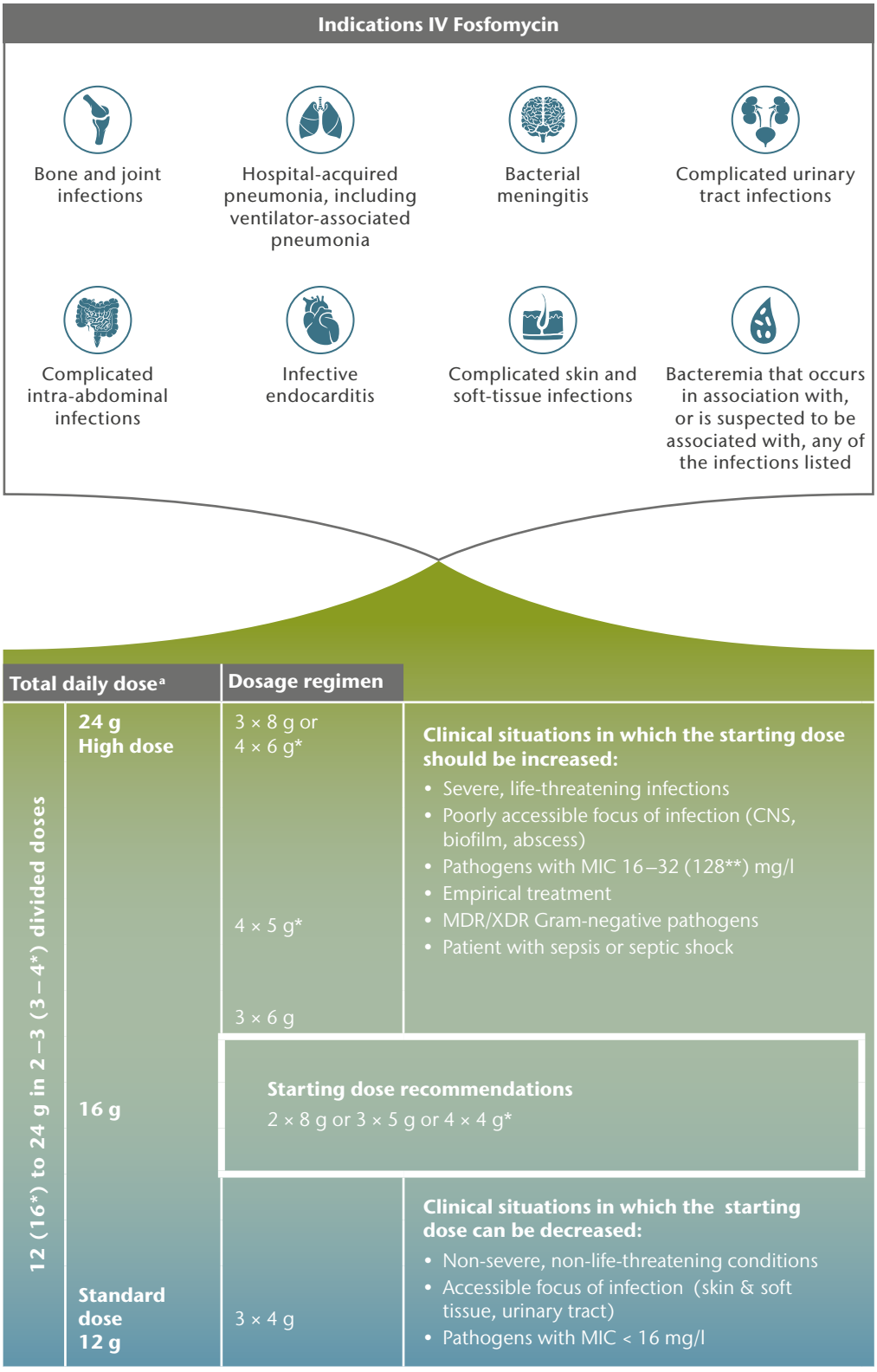
Indication	Daily dose
Complicated urinary tract infections (Section 3.2)	12–24 g[a] in 2–3 divided doses
Infective endocarditis (Section 3.3)	12–24 g[a] in 2–3 divided doses
Bone and joint infections (Section 3.4)	12–24 g[a] in 2–3 divided doses
Hospital-acquired pneumonia, including ventilator-associated pneumonia (Section 3.5)	12–24 g[a] in 2–3 divided doses
Complicated skin and soft-tissue infections (Section 3.6)	12–24 g[a] in 2–3 divided doses
Bacterial meningitis (Section 3.7)	16–24 g[a] in 3–4 divided doses
Complicated intra-abdominal infections (Section 3.8)	12–24 g[a] in 2–3 divided doses
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above (Section 3.9)	12–24 g[a] in 2–3 divided doses

Individual doses must not exceed 8 g.

[a]The high-dose regimen in 3 divided doses should be used in severe infections expected or known to be caused by less susceptible bacteria.

There are limited safety data in particular for doses in excess of 16 g/d. Special caution is advised when such doses are prescribed.

What dose for your patients? Watch the clinical situation



a Dosing for adults and adolescents ≥ 12 years of age (≥ 40 kg) with normal renal function (creatinine clearance > 80 mL/min); * Bacterial meningitis only; ** *P. aeruginosa*

Figure 17: Fosfomycin dose adjustment depending on the clinical and microbiological situation.

Given its low toxicity, good tolerability, and the predictive plasma levels after i. v. administration, fosfomycin has a broad dosing range of 12 g (16 g in bacterial meningitis) to 24 g per day that allows flexible dosing depending on the clinical and microbiological situation. The standard starting dose recommendations for intravenous fosfomycin are 15 or 16 g per day divided into 2–3 (4 in bacterial meningitis) single doses, provided that fosfomycin is used in combination therapy. However, depending on the patient's clinical conditions or information that are already available at start of treatment or become available later on during treatment, this starting dose recommendation should be revaluated and adjusted, if necessary (Figure 17).

In non-severe, non-life-threatening situations and infections with accessible focus (e. g., cUTI or cSSTI without abscesses) and/or highly susceptible pathogens (MIC < 16 mg/L) a lower daily dose of 12 g divided into 2–3 single doses might be sufficient if fosfomycin is combined with another antimicrobial agent.

The upper end of the dosing range of 18–24 g per day divided into 3–4 single doses should be considered in severe, life-threatening infections, infections with poorly accessible focus (e. g., biofilms, CNS, abscess), and /or borderline susceptible pathogens with MICs around 32 mg/L. Other circumstances that might require a high-dose regimen is empirical treatment, especially if multidrug-resistant/extensively drug resistant (MDR/XDR) gram-negative species are suspected. If monotherapy of patients with cUTI is considered, 18 g tid i. v. fosfomycin or more should be administered. Given that the pharmacokinetics in intensive-care patients with severe systemic inflammation, such as those with sepsis or septic shock, are altered towards an increased volume of distribution (V_d) and renal clearance, fosfomycin dosages of up to 24 g/d should be considered depending on the medical situation.

Bacterial meningitis represents a special case with regards to posology as it is *per se* considered a life-threatening condition with difficult-to-reach status requiring an intensified dosing regimen of 16–24 g/d divided into 3–4 single doses and always in combination with other antibiotics.

In general, no therapeutic drug monitoring is required for i. v. fosfomycin on account of its advantageous pharmacokinetic behaviour as well as its good safety profile.

Table 16: Fosfomycin dosage guidelines for children.

Age/weight	**Daily dose**
Premature neonates (age[a] <40 weeks)	100 mg/kg BW in 2 divided doses
Neonates (age[a] 40–44 weeks)	200 mg/kg BW in 3 divided doses
Infants 1–12 months (up to 10 kg BW)	200–300[b] mg/kg BW in 3 divided doses
Infants and children aged 1–12 yr (10–40 kg BW)	200–400[b] mg/kg BW in 3–4 divided doses

[a]Sum of gestational and postnatal age. [b]The high-dose regimen may be considered for severe infections and/or serious infections (such as meningitis), in particular when known or suspected to be caused by organisms with moderate susceptibility.

Dosage in paediatric populations

In children, the daily i. v. fosfomycin dosage is expressed in terms of body weight and age (post-menstrual age defined as sum of gestational age and postnatal age) as shown in Table 16. These dosing recommendations apply for all indications. However, the above considerations on the choice of a standard- or high-dose regimen for adult patients can be expanded to the paediatric population as well. High-dose regimen in infants ≥1 month correspond to daily doses of 300 mg/kg body weight (BW) and for children ≥1 yr to daily doses of 400 mg/kg BW. Neonates and premature neonates should receive a standard daily dose of 200 or 100 mg/kg BW, respectively. No dose recommendations can be made for children with renal impairment.

Dosage in renal insufficiency

Patients with impaired renal function require adjustment of fosfomycin dosage, depending on the degree of renal impairment (see Table 17). In patients with impaired renal function, dose titration should be based on creatinine clearance. Creatinine clearance in adults is calculated using the Cockroft and Gault formula:

$$\text{Creatinine clearance in men [mL/min]} = \frac{\textbf{(140 – age [yr]) × body weight [kg]}}{\textbf{72 × serum creatinine [mg/dL]}}$$

Creatinine clearance in women is obtained by multiplying the male value by 0.85.

Table 17: Fosfomycin dosage table for patients with impaired renal function.

$CL_{CR\ patient}$	$CL_{CR\ patient}/CL_{CR\ normal}$	Daily dosage recommended[a]
40 mL/min	0.333	70% (in 2–3 divided doses)
30 mL/min	0.250	60% (in 2–3 divided doses)
20 mL/min	0.167	40% (in 2–3 divided doses)
10 mL/min	0.083	20% (in 1–2 divided doses)

[a]The dose is expressed as a proportion of the dose that would have been considered appropriate if the patient's renal function were normal. The first dose should be increased by 100% (loading dose), but must not exceed 8 g.

Patients undergoing renal replacement therapy

Patients undergoing chronic intermittent dialysis (every 48 h) should receive 2 g of fosfomycin at the end of each dialysis session. On day without dialysis the patients should receive a fosfomycin dosage depending on their renal clearance (GFR) only in case there is still residual renal activity (CL ≥ 10 mL/min).

During continuous veno-venous haemofiltration (post-dilution CVVHF), fosfomycin is effectively eliminated. Patients undergoing post-dilution CVVHF will not require any dose adjustment. A study investigating 12 patients undergoing CVVHF with standard polyethylene sulfone haemofilters with a membrane surface of 1.2 m^2 and a mean ultrafiltration rate of 25 mL/min yielded a mean plasma clearance and a plasma elimination half-life of 100 mL/min and 12 h, respectively (Gattringer *et al.* [117]).

No clinical data exist for i. v. fosfomycin in patients undergoing pre-dilution CVVHF or other forms of renal replacement therapy.

Hepatic impairment

There are no data indicating that dose adjustment is necessary in patients with hepatic impairment. Fosfomycin can therefore be used in patients with all stages of hepatic impairment.

Elderly patients

The recommended doses for adults should also be used in elderly patients. The same dosage recommendations should be followed as described in Tables 15 and 17.

Method of administration

Fosfomycin is intended for intravenous administration. Each infusion should last no less than 15 min (fosfomycin 2 g), 30 min (fosfomycin 3 g, 4 g, 5 g), or 60 min (fosfomycin 8 g).

Preparation of solution for infusion

Intravenous fosfomycin must be reconstituted and diluted prior to administration. Prior to the reconstitution, the vial must be agitated to loosen the powder. This step facilitates and accelerates the solution procedure.

The reconstitution is performed by dissolving fosfomycin 2 g, 3 g, 4 g or 5 g in 20 mL water for injection, and fosfomycin 8 g in 40 mL water for injection. Dissolution of the substance will cause the solution to warm up slightly.

Caution: This intermediate solution is not intended for direct infusion. The solution must be withdrawn completely from the original vial and transferred into an infusion bag or other suitable infusion container for further dilution.

The dilution must be performed as follows: Transfer the reconstituted content of

- 2 g vials into an infusion container together with another 30 mL of solvent,
- 3 g, 4 g, and 5 g vials into an infusion container together with another 80 mL of solvent,
- 8 g vials into an infusion container together with another 160 mL of solvent.

Instead of water for injection, an equivalent volume of 5% or 10% glucose solution can be used.

Do not use sodium chloride solutions for reconstitution of fosfomycin due to the sodium content of the product. From a microbiological point of view, the infusion solution should be used immediately. If the prepared infusion solution is not used immediately, the user is responsible for the duration and conditions of storage which would normally be no longer than 24 hours at 2 to 8 °C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions. For a detailed description of the preparation procedure of fosfomycin please refer to the current Summary of Product Characteristics at the end of this monograph.

Duration of administration

Treatment duration should take account of the type of infection, the severity of the infection, and the patient's clinical response.

2.4.5.1 Toxicology and preclinical safety

- Fosfomycin has no genotoxic or carcinogenic potential or any impact on reproduction and fertility.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or toxicity to reproduction. No carcinogenicity data are available for fosfomycin.

Fertility

No data for humans are available. In male and female rats, the oral administration of fosfomycin up to 1 000 mg/kg/d did not impair fertility.

3 Indications and clinical data

3 Indications and clinical data

3.1 Summary

- Fosfomycin is a broad-spectrum antibiotic licensed for treating patients with:
  - Complicated urinary tract infections
  - Infective endocarditis
  - Bone and joint infections
  - Hospital-acquired pneumonia, including ventilator-associated pneumonia
  - Complicated skin and soft-tissue infections
  - Bacterial meningitis
  - Complicated intra-abdominal infections
  - Bacteraemia that occurs in association with or is suspected to be associated with any of the infections listed above

On account of its advantageous pharmacokinetic properties, comprehensive synergies with all other classes of antibiotics and good safety profile, i. v. fosfomycin is an excellent combination partner, in particular in severe life-threatening or difficult-to-treat infections. Recent clinical data show that fosfomycin is used irrespective of the localisation of the infection or resistance pattern of the pathogen (Putensen *et al.* [272]). The broad spectrum of indications is reflected in a systematic review of the available literature that summarised 128 published studies reporting the clinical use and efficacy of intravenous fosfomycin. Data on clinical use patterns were abstracted and analysed. Overall, intravenous fosfomycin use has been documented in more than 5 000 patients including more than 800 children (Grabein *et al.* [126]). An overview covering the most important indications for fosfomycin treatment is given in Figure 18, including most of the indications covered by the current licence for fosfomycin, i. e., sepsis/bacteraemia, respiratory tract infections including pneumonia, bone and joint infections, urinary tract infections, skin and soft-tissue infections, intra-abdominal infections, endocarditis and infections of the central nervous system (most importantly including meningitis). The following sections summarise the different indications for fosfomycin and include selected underlying clinical data.

3.2 Complicated urinary tract infections

- Monotherapy with i. v. fosfomycin (>16 g/d) is well suited for the treatment of complicated urinary tract infections (cUTI).
- Fosfomycin combination therapy is a valuable option for the treatment of complicated urinary tract infections caused by extended drug-resistant gram-negative pathogens (such as carbapenemase forming isolates).

Urinary tract infections are the most common bacterial infections. A complicated urinary tract infection is one associated with a condition such as specific anatomical or functional abnormalities of the genitourinary tract or the presence of an underlying disease, which increases the risk of infection and treatment failure (Bonkat *et al.* [46]).

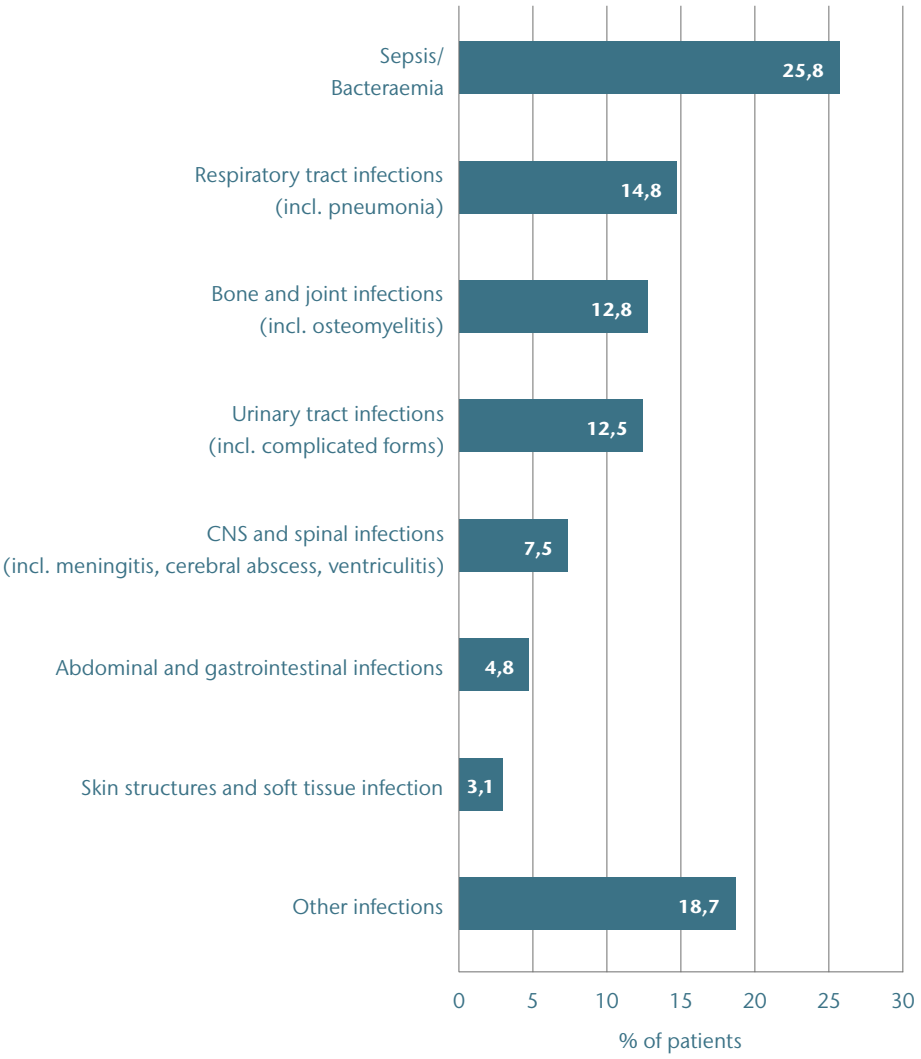


Figure 18: Patterns of clinical use of intravenous fosfomycin abstracted from 128 original publications including more than 5 000 patients treated (Grabein et al. [126]).

A broad range of bacteria can cause complicated urinary tract infections. The spectrum is much wider than in uncomplicated forms and bacteria are more likely to be resistant to a variety of antimicrobials. The most common species found in cultures are *Escherichia coli*, *Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp., *Serratia* spp., and *Enterococcus* spp. *Enterobacterales* are the most common pathogens, accounting for 60 to 75% of these infections, and *E. coli* is the most common single pathogen. However, *Pseudomonas aeruginosa* and gram-positive cocci (e. g., staphylococci and enterococci) may also play an important role, depending on the underlying condition. Optimal antimicrobial therapy needs to consider the severity of a patient's illness and conditions (such as allergies), local resistance patterns and – for targeted therapy – the results from urine cultures and susceptibility testing. Hospitalised patients with urinary tract infections showing systemic symptoms should be initially treated with intravenous antimicrobials based on local resistance data and possibly previous urine culture results. Piperacillin/tazobactam or ceftazidime are, besides other antibiotics, often seen as first-line therapy. The same holds for carbapenems, in particular in patients

with an increased likelihood of ESBL infection or for treatment of ESBL-producing enterobacteria. However, given the excellent susceptibility profile against enterobacteria and its pharmacokinetic properties in the urinary tract, fosfomycin can be regarded as an important alternative that may spare carbapenems and could replace carbapenems for the treatment of ESBL-producing *Enterobacterales* (Bouxom *et al.* [51], Karaiskos *et al.* [170]).

As fosfomycin is excreted via the kidneys in unaltered form, high urinary concentrations can be achieved, providing the rationale for its use. For *E. coli*, it is notable that a more acidic condition can improve the susceptibility to fosfomycin and reduce the MICs for fosfomycin. If a urinary isolate shows fosfomycin resistance under alkaline or neutral test conditions (as in broth or agar dilution), fosfomycin therapy of urinary tract infections is not necessarily futile. Martín-Gutiérrez *et al.* showed that an acidic urinary pH could considerably improve the susceptibility to fosfomycin in isogenic *Escherichia coli* strains bearing mutations in *glpT*, *uhpT*, *cyaA*, and/or *ptsI* (Martín-Gutiérrez *et al.* [215]). The MICs of these strains ranged between 32 and 1 024 mg/L when assessed in Müller-Hinton broth at a pH value of 8.0 under aerobic conditions. If the pH value of the broth was lowered to 5.0, a 2- to 64-fold reduction in MICs of strains with single mutations (e. g., from 32 to 0.5 mg/L in a *glpT* mutant), and an 8- to 64-fold reduction in MICs of strains with double mutations (e. g., from 1 024 to 16 mg/L in a *cyaA-glpT* doubly mutated strain) were noted. The effect was confirmed with clinical isolates and in urine containing glucose-6-phosphate (which would be released from tissues and erythrocytes in severe urinary tract infections). The reduction in MICs was less pronounced in urine as compared to broth media. Additionally, the growth rates of strains were significantly reduced under acidic conditions in culture. Thus, urinary *Escherichia coli* that demonstrated fosfomycin resistance under neutral or alkaline testing conditions may become susceptible and less biologically fit if the urine is acidified. This finding could have a practical impact in pregnant women or in patients under therapy with thiazides or uricostatic drugs (Martín-Gutiérrez *et al.* [215]).

Fosfomycin has been evaluated in several small studies of patients with conditions ranging from acute pyelonephritis to subacute or chronic urinary tract infection on the background of a variety of predisposing conditions (Ode *et al.* [247], Gobernado *et al.* [121], Allona *et al.* [10], Martinez *et al.* [214], Naber *et al.* [232], Kakizaki *et al.* [165], Amano *et al.* [12]). It is of note that the total daily doses of 3–6 g given in some of these studies do not reflect current clinical practice, where higher daily doses are recommended (Gobernado *et al.* [121], Allona *et al.* [10], Martinez *et al.* [214], Kakizaki *et al.* [165], Amano *et al.* [12]). The study of multidrug-resistant bacteria published by Dinh *et al.* reported favourable outcomes in 16/16 patients with urinary tract infections treated with combinations including fosfomycin (Dinh *et al.* [82]).

Results from a randomised, open, non-inferiority phase III clinical trial (FOREST study; NCT02142751) with 161 enrolled patients comparing fosfomycin vs. meropenem or ceftriaxone in bacteraemic urinary tract infections caused by extended-spectrum β-lactamases (ESBL) or quinolone-resistant *E. coli* has completed recruitment, but failed to achieve the planned number of patients. The patients were randomised to receive intravenous fosfomycin (4 g every 6 h) versus meropenem (1 g every 8 h) or ceftriaxone (1 g every 24 h). A switch to oral administration was allowed on day 5. Both groups were to complete 10 to 14 days of treatment (Rosso-Fernández *et al.* [283], Sojo-Dorado *et al.* [312]). Overall, 143 patients formed the mITT population (of initially planned 198 patients) with 70 patients who received fosfomycin and 73 patients the comparator (42 meropenem, 31 ceftriaxone). Both groups were similar in baseline features with a median age of 70 years and 26% of patients with sepsis or septic shock. A comparable proportion of 70% (49/70) of the patients

in the fosfomycin group achieved the study endpoint of clinical and microbiological cure compared with 79.4% (58/73) in the comparator group ($p = 0.1$). As the sample size of this non-inferiority study unfortunately could not be achieved, final conclusions regarding the non-inferiority of fosfomycin monotherapy compared to carbapenems or ceftriaxone cannot be drawn (Sojo-Dorado *et al.* [312]).

In 2017, a phase III clinical trial (ZEUS study, NCT02753946) was completed that studied the non-inferiority of parenteral fosfomycin (6 g/8 h) in monotherapy vs. piperacillin/tazobactam (4 g/0.5 g/8 h) for the treatment of complicated urinary tract infections (cUTI) or acute pyelonephritis (AP) in hospitalised patients (Kaye *et al.* [175]). The study involved 92 global sites across 16 countries and included a total of 465 patients with suspected or microbiologically confirmed cUTI or AP. 233 patients received i. v. fosfomycin, 231 patients were treated with piperacillin/tazobactam. Patients were treated for 7 days except for patients with concurrent bacteraemia who were treated for up to 14 days at the investigators discretion.

The m-MITT population consisted of 184 patients (65 males, 119 females, mean age 49.9 years) in the fosfomycin arm and 178 patients (67 males, 111 females mean age 51.3 years) in the piperacillin/tazobactam arm. Intravenous fosfomycin met the primary objective of non-inferiority compared with piperacillin/tazobactam, with an overall success rate of 64.7% (119/184 patients) vs. 54.5% (97/178 patients); the treatment difference in favour of fosfomycin was 10.2% (95% CI: –0.4, 20.8). Clinical cure rates at the test of cure visit (TOC) were high and similar between treatment groups (90.8 vs. 91.6%, respectively). Microbiological eradication favoured fosfomycin vs. piperacillin/tazobactam by approximately 10%, with 65.8 and 56.2% eradication in the fosfomycin and piperacillin/tazobactam group.

E. coli was the most commonly isolated pathogen with 72.3 and 74.7% in the fosfomycin and piperacillin/tazobactam groups, followed by *K. pneumoniae*. Overall, treatment arms were balanced in terms of number and type of baseline isolates bearing resistance characteristics (ESBL, Aminoglycoside-R, CRE, MDR) (34%). Among these resistant isolates, clinical cure rates were high, and eradication rates numerically favoured i. v. fosfomycin. Clinical cure rates were 93% (52/56) in the fosfomycin group and 93% (51/55) in the piperacillin/tazobactam group in patients infected with ESBL-pathogens, 97% (29/30) and 94% (29/31) in patients with aminoglycoside-resistant pathogens, 100% (9/9) and 85% (11/13) in patients with carbapenem-resistant pathogens, and 92% (34/37) and 90% (28/31) in patients with MDR pathogens, respectively. The microbiological eradication rates favoured fosfomycin over piperacillin/tazobactam, with rates of 55% (32/58) and 47% (27/57) in patients infected with ESBL pathogens, 67% (20/30) and 38% (12/32) in patients with aminoglycoside-resistant pathogens, 56% (5/9) and 31% (3/9) in patients with carbapenem-resistant pathogens, and 59% (23/39) and 37% (14/38) in patients with MDR pathogens, respectively (Kaye *et al.* [175])

Its renal elimination as unaltered drug that leads to high drug levels in the urogenital tract including kidneys and bladder combined with its antibacterial activity against urinary pathogens including MDR strains makes i. v. fosfomycin an ideal option for the treatment of patients with complicated urinary tract infections. Therefore, the S2k guideline of the German Paul-Ehrlich-Society for Chemotherapy recommends fosfomycin as an option for initial therapy of cUTI. Clinical data support the use of i. v. fosfomycin for the treatment of complicated urinary tract infections (acute or chronic) including pyelonephritis in patients with a variety of predisposing conditions both in monotherapy and in combination with other antibiotics.

3.3 Infective endocarditis (IE)

- Intravenous fosfomycin is an effective treatment of native and prosthetic-valve IE.
- Intravenous fosfomycin should be used in combination therapy only, e. g. with β-lactams, daptomycin, or vancomycin.
- Studies using fosfomycin combinations show rapid microbiological eradication.
- Intravenous fosfomycin is recommended by several national and European medical societies for the treatment of IE.

Infective endocarditis is defined as an infection of the endocardial surface of the heart or the heart valves. According to various studies, the incidence of IE in western countries ranges from 7.6 to 12.7/100 000 p. a. (Consilium Infectiorum [66]). One-year mortality amounts to about 30% and thus is still high (Cahill *et al.* [56]). In about 90% of all cases, a left-side IE is diagnosed and in only 10% of all cases a right-side IE, with a regularly less progressive course. The aortic valve is affected in 35% of all cases, the mitral valve in 30% and both in 15% (Hoen *et al.* [151], Murdoch *et al.* [231]). In 7–25% (up to 40%) of all patients, a prosthetic valve is infected (Mestres *et al.* [221]). Staphylococci are the most important causative pathogens of IE with roughly 41% of all cases (followed by streptococci with 31%) and frequently susceptible to fosfomycin (Murdoch *et al.* [231]). The favourable characteristics of fosfomycin such as its very low plasma protein binding allow its wide distribution to difficult-to-treat infection sites. In aortic and mitral valves, it reaches therapeutic drug levels above the MIC of susceptible pathogens within 30 min after the end of infusion of 5 g even in calcified and severely destructed tissue (Hirt *et al.* [149]). Other characteristics of fosfomycin, such as the lack of clinically relevant drug interactions or of any antagonism with other concomitantly administered antibacterial agents, and the fact that no therapeutic drug monitoring is required also support its use for this indication.

The use of i. v. fosfomycin has been studied in several clinical trials including patients with IE caused by staphylococci. Core data of case series and prospective multicentre studies collecting clinical data of fosfomycin efficacy as part of an antibiotic combination regimen are listed in Table 18. Del Rio *et al.* investigated the efficacy of fosfomycin in combination with imipenem as a rescue therapy in a clinical trial including 12 patients with IE due to *S. aureus* (del Río *et al.* [75]). Overall, blood cultures were negative 72 hours after the first dose and the success rate was 69% in these patients. The authors concluded that fosfomycin plus imipenem was an effective combination when used as rescue therapy for MRSA bloodstream infections. The same conclusion was drawn by Pericàs *et al.* who analysed fosfomycin plus imipenem in the treatment of IE due to MRSA (Pericàs *et al.* [260]). Another publication reports that fosfomycin in combination therapy is a good alternative to treat these difficult-to-treat infections, allowing the rapid control of bacteraemia and achieving better outcomes (del Río *et al.* [76]). Recent interim data from a large prospective, non-interventional, and monitored European multicentre study (FORTRESS) report high clinical success in 79% (11/14) of patients with IE predominantly caused by MSSA. The proportion of foreign-body associated IE was high (10/14, 71%) and even here clinical success was achieved in the majority of patients (7/10, 70%). As with other studies, microbiological cure was achieved in all patients with IE (14/14, 100%) (Hagel *et al.* [138]).

Table 18: Case series and prospective clinical studies investigating the efficacy of fosfomycin combination therapy in infective endocarditis.

First author [Ref.]	Age of pts. (yr)	*N*	Study design	Indication	Therapy regimen	Dose of fosfomycin	Clinical outcome	Microbiological outcome
Bär [27]	35–78	5	Case series	Aortic-valve endocarditis (*n* = 1); postoperative mitral-valve endocarditis (*n* = 1); pacemaker-associated MSSA endocarditis (*n* = 3); pat. with renal insufficiency	2nd- and 3rd-line fosfomycin plus vancomycin, rifampicin, and/or cefazolin	3 g bid or 2 g tid (6 g/d) for 1–5 weeks	Clinical success in 4/5 (80%) pts., one relapse	NR
del Río [75]	25–87	16	Multicentr. prosp.	MRSA endocarditis (*n* = 12); vascular device infection (*n* = 2); complicated bacteraemia (*n* = 2)	2nd-line fosfomycin plus Imipenem	2 g qid (8 g/d) for 4 weeks (median; range 4–75 d)	Clinical success 11/16 (68%), 5 pts. died	Sterile BC on day 3
Hagel [138]	64	14	Open multicentr. prosp.	Native and foreign-body-associated IE	Fosfomycin combination, mostly with β-lactams, vancomycin or daptomycin	15 g/d	Clinical success 11/14 (79%) pat., 4/4 pat. w/o foreign body, 7/10 (70%) pat. with foreign body	All 14 patients with sterile BC at EOT
Miró [226]	53, 54, 71	3	Case series	Aortic homograft MSSA endocarditis (*n* = 1); left-sided MRSA endocarditis with perivalvular abscesses (*n* = 2)	2nd-line fosfomycin plus high-dose daptomycin	2 g qid (8 g/d) for 6–8 weeks	Alive at 12, 12, and 6 months after therapy, respectively	Sterile BC on day 14, 14, and 30, respectively

Table 18: Case series and prospective clinical studies investigating the efficacy of fosfomycin combination therapy in infective endocarditis.

First author [Ref.]	Age of pts. (yr)	*N*	Study design	Indication	Therapy regimen	Dose of fosfomycin	Clinical outcome	Microbiological outcome
Pericàs [260]	>80	15	RCT	Complicated *S. aureus* bacteraemia and infective endocarditis	Fosfomycin plus imipenem vs. vancomycin monotherapy	2 g qid 6 h	Fosfomycin plus imipenem 4/8 (50%); vancomycin 3/7 (43%)	Sterile BC at ≤3 d in fosfomycin group
Putensen [272]	mean 59 (ITT)	9	Open multicentr. prosp.	Complicated *Staphylococcus* bacteraemia and infective endocarditis (*n* = 7), 1 *E. faecalis* IE	Fosfomycin combination therapy with β-lactams, vancomycin, rifampicin and aminoglycoside	7/9 ≤ 15 g/d, 2/9 >15 g/d	Clinical success 6/9 (67%, cPP)	Sterile BC (4/4, mPP)

BC: Blood culture; EOT: End of treatment; NR: Not reported; RCT: Randomised controlled trial.

Overall, fosfomycin was predominantly used in older patients, severe cases and unsuccessful pre-treated patients. The efficacy rates in case series and clinical studies of 62 difficult-to-treat patients were favourable and ranged from 50 to 80%. All patients showed a sterilisation of blood cultures within 3 treatment days according to available data (Table 18).
Several case reports document the successful use of fosfomycin as a part of an antibiotic combination regimen in the therapy of staphylococcal endocarditis, including MRSA (Aoyagi *et al.* [17], Cañamares-Orbis *et al.* [58], Chen *et al.* [61], de Boutin *et al.* [73], Fukuda *et al.* [113]).

According to the 2015 guidelines of the European Society of Cardiology for the management of infective endocarditis, fosfomycin in combination with daptomycin has been recommended for treating staphylococcal endocarditis as an alternative therapy for patients allergic against penicillin and infected with methicillin-susceptible or methicillin-resistant staphylococci (Habib *et al.* [135]). This treatment option is also recommended in a guideline on the diagnosis and treatment of bacteraemia and endocarditis due to *S. aureus* by the Spanish Society of Clinical Microbiology and Infectious Diseases (Gudiol *et al.* [130]). The S2k guideline of the German Paul-Ehrlich-Society for Chemotherapy recommends a combination of daptomycin and fosfomycin for the treatment of staphylococcal prosthetic-valve IE (Bodmann *et al.* [43]). According to the Pocket Guide to Diagnosis & Treatment of Infective Endocarditis provided by the PRO-IMPLANT Foundation, fosfomycin is a recommended combination partner in the treatment of MSSA/MRSA endocarditis of native and prosthetic valves (Conen *et al.* [65]).

Although doses below 12 g, particularly the regimen 2 g q6h, are recommended in clinical guidelines (Habib *et al.* 135, Gudiol *et al.* [130], Bodmann *et al.* [43]) for the treatment of IE, the basis for these dosage recommendations remains unclear. The timeliness of the data is often questionable and overall it is obvious that these recommendations lack a systematic basis. In the context of the recently completed re-evaluation procedure of fosfomycin medicines under the leadership of the European Medicines Agency it was concluded that a total daily dosage of 12–24 g, which is already international standard practise in other indications, could be safely extended to infective endocarditis. However, as the treatment in the case of infective endocarditis needs to be prolonged (4 to 6 weeks for IE caused by MRSA in native-valve endocarditis and ≥6 weeks in prosthetic-valve endocarditis), sodium and potassium blood levels need to be monitored regularly. Table 18 summarises the existing evidence for the use of i. v. fosfomycin for the treatment of infective endocarditis from (controlled) studies with prospective design or case series.

3.4 Bone and joint infections

- In patients with osteomyelitis, spondylodiscitis, septic arthritis, and prosthetic joint infections, combination therapies with i. v. fosfomycin show high clinical success.
- Intravenous fosfomycin is recommended for empiric and targeted first-line treatment of native and foreign-body-associated osteoarticular infections.

Infections of the bones and joints are serious health problems causing bone death, soft-tissue compromise, functional impairment, and considerable morbidity. They encompass a large spectrum of different diseases which are classified with respect to the duration of disease (acute/chronic), their anatomic location (long bones/vertebrae), and the presence of an implant or diabetes. Their prevalence is steadily increasing, mainly due to the rising life expectancy of the population and the increasing use of bone fixation devices and prosthetic joints (Zimmerli [360], McNally *et al.* [218]). Among pathogenic microorganisms, *Staphylococcus aureus* is by far the most common one involved (Lew *et al.* [195]).The key to successful management is a multidisciplinary approach that covers the diagnostic and therapeutic treatment and requires antibiotics and often surgery. Randomised clinical studies are mostly missing (Zimmerli [360]). Table 19 gives an overview of selected studies involving the use of fosfomycin in bone and joint infections.

3.4.1 Osteomyelitis and septic arthritis

Osteomyelitis is an inflammatory process within bone, bone marrow, and surrounding soft tissue that develops secondary to an infection with bacterial organisms. It can be haematogenous in origin, as in most paediatric cases, or it can develop after surgery or trauma (Zimmerli [360], Scheffer *et al.* [296]). Most cases of haematogenous osteomyelitis are caused by *Staphylococcus aureus* and other gram-positive cocci. The spectrum of pathogens in post-operative or post-traumatic osteomyelitis also includes gram-negative bacteria and anaerobes. An acute infection may respond to a treatment based exclusively on antibiotics. In contrast, in chronic osteomyelitis a combined antimicrobial and surgical approach is always necessary, because a debridement of destructed bone is required (Zimmerli [360]). A particular problem in the treatment of bone infections are late relapses, which can occur even after many symptom-free years.

Septic arthritis is a joint inflammation secondary to a bacterial aetiology. It is usually monoarticular, involving one large joint such as the hip or knee. However, polyarticular septic arthritis involving multiple or smaller joints may also occur. Septic arthritis is an orthopaedic emergency that can cause significant joint damage involving the loss of cartilage and leading to increased morbidity and mortality. Early diagnosis and treatment are crucial for preserving joint function (Momodu *et al.* [227]).

Fosfomycin with its bactericidal mode of action is a suitable antibiotic for the treatment of osteoarticular infection. It penetrates rapidly into soft and bone tissues including both cortical and cancellous bone and even sequester, and entirely equilibrates with plasma approximately 3 h post-infusion (Section 2.4.1.5). Fosfomycin covers the relevant spectrum of pathogens (Section 2.4.2.1), and its intracellular activity against them furthermore counteracts the risk of persistent infections and thus recurrence (Section 2.4.1.2). In combination with other antimicrobials, fosfomycin mostly acts synergistically or additively (Section 2.4.2.4). Due to its excellent safety profile (Section 4), fosfomycin offers a reasonable treatment option for the therapy of osteoarticular infection also in children.

The efficacy of i. v. fosfomycin in osteomyelitis with different aetiologies has been studied intensely. In patients with chronic post-traumatic or post-operative osteomyelitis receiving fosfomycin as therapeutic agent, clinical success was reported in 74% (Meißner *et al.* [219]). It should be noted that these patients had a long history of disease and had been extensively – and unsuccessfully – treated before with up to 12 antibiotic courses and on average 2.4 operations (Meißner *et al.* [219]). In a cohort with 75 patients suffering from recurrent chronic post-operative osteitis, fosfomycin was administered in addition to surgical revision and local antiseptic treatment. 26 cases were monobacterial, 49 patients had polymicrobial infections. After two weeks of fosfomycin therapy, the cultures were sterile in 86.7% of the patients. Furthermore, only 9.3% of the patients experienced recurrence in the fosfomycin group within 18 months after the intervention, whereas in the control group without fosfomycin, 23.9% relapsed (Roth *et al.* [284]). In paediatric populations with haematogenous osteomyelitis or septic arthritis, fosfomycin has also been successfully used (Corti *et al.* [68], Badelon *et al.* [23], Fitoussi *et al.* [102], Stricker *et al.* [319]).

Further documented cases support the use of i. v. fosfomycin in osteoarticular infection in adults, including even involvement of difficult-to-treat pathogens such as carbapenemase-producing *Klebsiella pneumoniae* (Baron *et al.* [32], Baron *et al.* [29]). In multidrug-resistant osteoarticular infections, Dinh *et al.* reported favourable outcomes in 82.6% of patients treated for a median duration of 54 days with combinations including fosfomycin (Dinh *et al.* [82]).

Recently, similar clinical success rates of 85.7% were reported by Putensen *et al.* for the treatment of bone and joint infections with fosfomycin in combination (Putensen *et al.* [272]).

Data from these studies suggest that intravenous fosfomycin is an effective combination partner for the treatment of bacterial bone infections of various origins. According to the Summary of Product Characteristics, the recommended daily dosage of fosfomycin for this indication is 12–24 g divided into 2–3 doses (Section 2.4.5.).

The S2k guideline of the German Paul-Ehrlich-Society for Chemotherapy recommends fosfomycin as a combination partner for the first-line treatment of gram-positive osteomyelitis with haematogenous, post-traumatic, and post-operative origin, respectively, as well as in sternal osteomyelitis caused by staphylococci. In addition, in cases of haematogenous osteomyelitis with gram-negative *Enterobacterales*, and in mixed infections of post-operative osteomyelitis, the combination with fosfomycin is further recommended as a treatment option (Bodmann *et al.* [43]).

According to the Pocket Guide to Diagnosis & Treatment of Septic Arthritis provided by the PRO-IMPLANT Foundation, fosfomycin is a recommended combination partner in the empiric treatment of septic arthritis of native joints as well as after ligament repair, and in targeted treatment of *S. aureus* including MRSA, and enterococci, respectively (Margaryan *et al.* [211]).

Table 19: Case series and prospective clinical studies investigating the efficacy of fosfomycin in bone and joint infections.

First author [Ref.]	Age of pts. (yr)	*N*	Study design	Indication	Therapy regimen	Dose of fosfomycin	Clinical outcome	Microbiological outcome
Badelon [23]	0–13 (Ø 3.5)	23	Prospective	Osteomyelitis (*n* = 8); arthritis (*n* = 15)	Fosfomycin plus cefotaxime, amoxicillin, vancomycin, amikacin and/or gentamicin	100 mg/kg/d	100% cured	NR
Baron [29]	Ø 39	20	Open non-comparative trial	Osteomyelitis (*n* = 12); osteoarthritis (*n* = 8)	Fosfomycin plus oxacillin (or methicillin), vancomycin, others	200 mg/kg/d	Osteomyelitis: 11/12 cured/improved, 1 failure Osteoarthritis: 8/8 cured/improved	NR
Corti [68]	0.1–15.5 Ø 6.5	103	Retrospective	Acute haematogenous osteomyelitis (no primary surgical treatment)	Group 1 (22%): Fosfomycin monotherapy; Group 2 (46%): Fosfomycin plus penicillin or clindamycin; Group 3 (32%): Other agents	Group 1: 200 mg/kg/d (Ø 2.5 weeks) Group 2: 200 mg/kg/d (Ø 3.1 weeks)	Clinical success in 100%, normalisation of CRP and ESR within 1 week, 1 pt. each of Group 2 and 3 relapsed	NR

Table 19: Case series and prospective clinical studies investigating the efficacy of fosfomycin in bone and joint infections.

First author [Ref.]	Age of pts. (yr)	*N*	Study design	Indication	Therapy regimen	Dose of fosfomycin	Clinical outcome	Microbiological outcome
Dinh [82]	Ø 5 (children); Ø 67 (adults)	32	Prospective	Osteoarticular infection	Fosfomycin combination therapy, e. g. glycopeptides, cephalosporins, carbapenem, others	3–4× 4 g/d	Favourable overall global outcome 82.6%	NR
Fitoussi [102]	NA	18	Retrospective	Wrist osteomyelitis	Fosfomycin plus cephalosporins	ND	16 pts. (89%) cured, 2 pts. with orthopaedic sequelae	NR
Karbysheva [171]	18–86	45	Prospective	Periprosthetic joint infection	Fosfomycin combination therapy	5 g every 8 h	Relapse-free survival after 1 yr was 88.5% (95% CI 86.5–100%)	NR
Meißner [219]	17–78	60	Prospective	Chronic post-traumatic or post-operative osteomyelitis	2nd- and 3rd-line fosfomycin monotherapy	5 g every 8 h (15 g/d) for Ø 13.9 d (5–28 d)	After 7–53 months: 54.7% very good (without war-wounded patients: 62.8%), 3.8% good, 15.1% satisfactory, 26.4% failure	NR
Putensen [272]	Ø 59	23	Prospective	Bone and joint infections	Fosfomycin combination therapy	Standard dose 15 g/d or less	Clinical success 85.7%	Microbiological eradication 100% (n = 13)
Renz [273]	30–90	25	Retrospective	Enterococcal periprosthetic joint infection	Fosfomycin combination therapy, e. g. penicillin derivative, vancomycin or daptomycin	5 g every 8 h	Treatment success 95%	NR

First author [Ref.]	Age of pts. (yr)	*N*	Study design	Indication	Therapy regimen	Dose of fosfomycin	Clinical outcome	Microbiological outcome
Roth [284]	NR	75	Prospective	Chronic post-operative osteitis, therapeutic failures	Fosfomycin monotherapy (+ antiseptic wound care)	5 g every 12 h (*n* = 28), 5 g every 8 h (*n* = 47); Ø 13.6 d	Recurrence in 9.3% (after ≥18 months)	Cumulative number of pts. with negative results: day 7: 36; day 14: 65; day 21: 70 (5 patients remained positive)
Stengel [315]	Ø 62.9	52	Prospective	Diabetic foot infections (limb-threatening)	Fosfomycin plus meropenem, amoxicillin/sulbactam, clindamycin, ciprofloxacin, others	8–24 g/d	48/52 (92.3%) limb salvage (primary endpoint); 13/52 cured; 31/52 markedly improved; 4/52 inconclusive; 4 failure	NR
Stöckl [318]	14–80 (Ø 60)	40	Retrospective	Spondylodiscitis	Fosfomycin plus cephalosporins, clindamycin, rifampicin, vancomycin and/or metronidazole	8–24 g/d	Clinical success 87.5%	

ND: Not determined; NR: not reported.

3.4.2 Spondylodiscitis

Spondylodiscitis, or vertebral osteomyelitis, is characterised by infection of the vertebral body and intervertebral disc space. The incidence has been estimated to range from 0.3 to 6.5 cases/100 000 persons, thus making it a rare disease with an incidence that generally increases with age. Spondylodiscitis most often results from haematogenous seeding, but can also be acquired during spine surgery or contiguous spread from an infection in the adjacent soft tissue. *Staphylococcus aureus* is the most common microorganism implicated in pyogenic vertebral osteomyelitis, followed by *E. coli*. In spinal-implant-associated infections, coagulase-negative staphylococci and *Cutibacterium acnes* are the predominant causative pathogens (Zimmerli [361]). Any initial empiric antibiotic therapy of spondylodiscitis should cover staphylococci, streptococci, enterococci, and gram-negative bacilli as the most common pathogens (Palmowski *et al.* [253]). For native spondylodiscitis, a 6-week antibiotic treatment seems appropriate, whereas biofilm-associated infections need to be treated up

to 12 weeks, in either case intravenously for the initial 1–3 weeks. Evidence-based guidelines still do not exist for the appropriate antimicrobial treatment of vertebral osteomyelitis due to the lack of randomised controlled trials (Palmowski *et al.* [253], Jung *et al.* [162]). It is expected that suitable agents need to possess good bone penetration capabilities (Fleege *et al.* [104], Jung *et al.* [162]), which holds true for fosfomycin (Section 2.4.1.5). Fosfomycin even acts bactericidal at lower pH and under anaerobic conditions, which is advantageous in complicated cases with the presence of paravertebral, epidural, or psoas abscesses, which fosfomycin is able to penetrate as well (Section 2.4.1.5; Haag [134], Hamilton-Miller [140]). A stabilised spondylodiscitis is challenging to treat due to the formation of biofilms on foreign material. However, fosfomycin with its broad antibacterial spectrum covering most of the causative species is also able to eradicate biofilm-embedded pathogens (Sections 2.4.2.1 and 2.4.2.3). These characteristics, together with its synergistic action when combined with all classes of antibiotics and lack of clinically relevant drug interactions, make i. v. fosfomycin a well-suited candidate for spondylodiscitis therapy (Section 2.4.2.4).

Fosfomycin has been studied clinically in 40 patients with haematogenous spondylodiscitis (Stöckl *et al.* [318]). 65% of these patients underwent unsuccessful antimicrobial therapy with β-lactams, clindamycin, and/or rifampicin prior to inclusion into the study. The most frequent complications were epidural abscesses (28%), psoas abscesses (18%), and abscesses at other locations (20%). In 50% of patients, punctures, abscess drainages, or surgical procedures were required. Causative pathogens could be identified in 73% of patients, they were predominantly staphylococci, *Streptococcus* spp., or *Escherichia coli*. Clinical success was reported in 87.5% of patients treated with doses of 8–24 g fosfomycin per day over a median period of 24 days in combination with one or two additional antibiotics. It should be mentioned that all therapy failures were associated with a lower dose of fosfomycin of 4 g twice daily (Stöckl *et al.* [318]). Thus, according to the Summary of Product Characteristics, a daily dosage of 12–24 g fosfomycin is indicated for the treatment of spondylodiscitis (Section 2.4.5). In another study involving 34 patients with vertebral osteomyelitis after disc surgery, all participants were clinically cured following combination treatment with fosfomycin plus either ceftriaxone, clindamycin, or amoxicillin/clavulanic acid (Wurm [354]).

Fosfomycin is recommended in current guidelines for empiric as well as for targeted first-line treatment of haematogenous spondylodiscitis with and without implants (Bodmann *et al.* [43], Fleege *et al.* [104], Jung *et al.* [162]).

The importance of biofilm-active substances – including fosfomycin – in post-operative spinal implant-associated infections has recently been investigated. Their use was significantly associated with a better treatment outcome and less post-operative pain (Köder *et al.* [181]). Based on these findings, empiric and targeted combination with fosfomycin is recommended in post-operative spinal implant infections by staphylococci, enterococci, and gram-negative pathogens (Palmowski *et al.* [253]).

3.4.3 Prosthetic joint infections (PJI)

With a steadily increasing number of implantations, the number of PJI cases also rises continuously. Periprosthetic joint infections occur in 1–2% of primary and in 4% of revision arthroplasties. When missed or undertreated, PJI lead to persistence of infections and multiple surgical revisions causing poor function or disability, thus considerably impairing quality of life (Izakovicova *et al.* [158]).

Microorganisms causing foreign-body-related infections form biofilms on the surface of the implant, rendering the associated infection challenging to treat and enabling even low-virulence microorganisms such as coagulase-negative staphylococci or *Cutibacterium* spp. to cause infection. Staphylococci (*S. aureus* and coagulase-negative staphylococci, especially *S. epidermidis*) account for more than 50% of all episodes of periprosthetic hip and knee infection. Approximately 20% of PJI cases are polymicrobial, and about 7% are culture-negative (Zimmerli [360]).

Management of PJI requires interdisciplinary treatment strategies including multiple surgical revisions and long-term antimicrobial treatment for up to 12 weeks. Based on recent studies, any i. v. therapy should be limited to approximately 2 weeks post-operatively (Izakovicova *et al.* [158], Li *et al.* [198]). In multistage procedures, fosfomycin is a useful option for use during the prosthesis-free interval. Its highly bactericidal and synergistic activity (Section 2.4.2.4) assists the goal of maximum reduction of the pathogen, while at the same time enabling treatment of soft-tissue infections and osteomyelitis, for which fosfomycin is both approved (Section 3.1; Izakovicova *et al.* [158]). In one-stage procedures or prosthesis retention as well as following reimplantation, respectively, the combination with fosfomycin as biofilm-active antibiotic (Section 2.4.2.3) enables the eradication of pathogens and thus provides protection of the implant (Izakovicova *et al.* [158]). These characteristics together with its excellent tissue penetration and broad antimicrobial spectrum covering also polymicrobial infections make fosfomycin a highly attractive option for PJI therapy (Sections 2.4.1.5 and 2.4.2.1).

The use of fosfomycin as part of the treatment algorithm as described above has been clinically studied. Renz *et al.* evaluated characteristics and outcome of enterococcal PJI, which were previously classified as "difficult to treat" due to the lack of biofilm-active antibiotics and high treatment failure rates. However, fosfomycin was identified as promising agent against planktonic and adherent *E. faecalis* both *in vitro* and in animal model data (Section 2.4.2.3). The authors propose a cut-off for enterococci and intravenous fosfomycin of 128 mg/L in daily routine, which is extrapolated for the use of fosfomycin as combination partner in infections caused by wild-type isolates of *Pseudomonas* spp. The reason for that is that EUCAST does not provide a breakpoint for enterococci and fosfomycin, since treatment of enterococcal infections with fosfomycin in monotherapy is not recommended. Using the aforementioned fosfomycin MIC cut-off of 128 mg/L, 21 of 22 enterococci isolates (96%) were susceptible to fosfomycin. About half of all enterococcal PJI were polymicrobial infections. Intravenous fosfomycin was applied at a dosage of 5 g every 8 h for a median duration of 14 days (range 3–90 d). Treatment success was defined as absence of relapse or persistence of PJI due to enterococci or death related to enterococcal PJI. When intravenous fosfomycin was included in the treatment regimen, the treatment success was numerically higher than without intravenous fosfomycin (95% vs. 80%), the difference did not reach statistical significance, however (Renz *et al.* [273]).

The efficacy and safety of i. v. fosfomycin in periprosthetic joint infection is currently investigated in a prospective multicentre study (PROOF) comprising 226 patients. According to a standardised algorithm, fosfomycin-based combinations followed by oral antibiotics for a total of 12 weeks are evaluated in a pathogen- and surgery-specific mode. Infection outcome based on clinical, laboratory, and radiological evaluation is assessed as the proportion of infection-free patients within 1 year (EudraCT 2016-002673-35). Karbysheva *et al.* presented first preliminary results of 45 PROOF patients at the ECCMID congress in Amsterdam in 2019. Pathogens isolated were *Staphylococcus aureus* (n = 13), coagulase-negative staphylococci (n = 17), *Enterococcus* spp. (n = 5), *Streptococcus* spp. (n = 3), and gram-negatives (n = 2). Cultures were negative in 9 patients and polymicrobial in 2 patients. The relapse-free survival rate after 1 year was 88.5% (Karbysheva *et al.* [171]).

The importance of biofilm-active therapy in periprosthetic joint infection with fosfomycin as a part of the treatment algorithm has been evaluated recently. Infection-free survival after 1 year was better for patients receiving biofilm-active antibiotics compared to those who did not (83% vs. 70%; $p = 0.040$) and remained superior after 2 years (67% vs. 48%; $p = 0.038$). In addition, biofilm-active antibiotic therapy was associated with lower pain intensity and improved joint function in patients with knee PJI prospectively included in this cohort study (Gellert *et al.* [118]).

Consequently, current recommendations and guidelines list fosfomycin as a recommended combination partner for the treatment of periprosthetic joint infections (Izakovicova *et al.* [158], Li *et al.* [196], Bodmann *et al.* [43], Ariza *et al.* [19]). Furthermore, infections after fracture fixation also require biofilm-active therapy due to the insertion of orthopaedic implants. However, as studies solely focusing on this indication are scarce, targeted antibiotic treatment strategies are extrapolated from guidelines for other implant-related infections (i. e., PJI) (Depypere *et al.* [78]). Fosfomycin is thus recommended for the treatment of fracture-related infections caused by staphylococci, enterococci, and gram-negatives (Steinmetz *et al.* [314]).

Even in difficult-to-treat infections with the presence of foreign material and/or challenging pathogens, combination therapy with fosfomycin applied in a dosage of 12–24 g divided into 2–3 doses (Sections 2.4.5 and 3.1) represents a recommended treatment option with good clinical evidence.

3.4.4 Osteomyelitis occurring in association with diabetic foot infections

Diabetic foot infections are the major cause of lower limb amputations in developed countries. Staphylococci, group A streptococci, and enterococci are the usual pathogens responsible for this potentially life-threatening infection. Deep infections that affect the bone may also involve gram-negative *Enterobacterales*. In necrotising processes and gangrene, anaerobic pathogens must also be considered (Esposito *et al.* [90], Graninger *et al.* [128]). Fosfomycin with its broad antimicrobial spectrum (Section 2.4.2.1) is well suited for the treatment of diabetic foot infections, which are usually polymicrobial (Graninger [128]). High penetration rates into bone, inflammatory lesions and abscessing tissue combined with its bactericidal efficacy even at lower pH support the use of fosfomycin in this indication (Schintler *et al.* [297], Sauermann *et al.* [295], Legat *et al.* [191], Haag [134]). Furthermore, its effect against staphylococci is even increased in the anaerobic environments that are typical of this condition (Hamilton-Miller [140]).

In 2001, a compassionate-use program was launched in 5 medical centres in Austria. 52 patients with severe diabetic foot infections with osteomyelitis (≥ Wagner grade 3) associated with a high risk of major amputation and failure of previous antibiotic treatment were enrolled (Stengel *et al.* [315]). Surgical measures at the discretion of the treating clinician were permitted during fosfomycin therapy. The primary endpoint of the study was major amputation. In 24 patients (46.2%), a mixed flora was detected. Fosfomycin was given as a second-line treatment at daily doses of 8–24 g, mostly in combination with β-lactams, ciprofloxacin, or clindamycin. Overall, the affected limb could be salvaged in 48 of the 52 patients (92.3%). Four patients showed an inconclusive response yet did not have to undergo amputation (Stengel *et al.* [315]).

Fosfomycin is recommended for targeted therapy of *S. aureus*, β-haemolytic streptococci, Enterobacterales, or anaerobes in patients suffering from severe diabetes mellitus associated with deep infected foot ulcer, as it reaches sufficiently high levels in soft tissue and adjacent bone regions (Bodmann *et al.* [43]).

In conclusion, fosfomycin has been proven to be highly effective in clinical practice. It represents a recommended treatment option for diabetic foot infections. Approved for the therapy of bone and joint infections and complicated skin and soft-tissue infections in a dosage of 12–24 g divided into 2–3 doses (Sections 2.4.5 and 3.1), fosfomycin enables an in-label treatment of diabetic foot infections, usually as a part of a combined antimicrobial approach.

3.5 Hospital-acquired pneumonia including ventilator-associated pneumonia

- Intravenous fosfomycin is well suited for the initial treatment of HAP and VAP especially in patients at risk for multiresistant pathogens.
- Real-life clinical data show high clinical success rates of fosfomycin combinations in patients with HAP or VAP.

Hospital-acquired pneumonia is an infection of the pulmonary parenchyma that develops within 48 hours or more after hospital admission and that was not incubating at the time of admission. Among nosocomial pneumonia, ventilator-associated pneumonia (VAP) develops in intensive care unit (ICU) patients who have been mechanically ventilated for at least 48 h. In Europe, nosocomial pneumonia is the second most common nosocomial infection and the most common nosocomial infection in ICUs (Bodmann *et al.* [43]). Nosocomial pneumonias are infections with the highest mortality rates (30–50%) and further complicated by various risk factors such as age, previous antibiotic treatment, immunosuppression, and ventilation (Bodmann *et al.* [43]). Early and effective antibiotic treatment is an important strategy to decrease the morbidity and mortality of patients with nosocomial pneumonia. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most common pathogens causing nosocomial pneumonias, followed by *Klebsiella pneumoniae* and *Escherichia coli* (Dahlhoff *et al.* [72]). Multidrug-resistant bacteria are often found in high-risk patients transforming nosocomial pneumonia into a difficult-to-manage infection. One major risk factor for MDR HAP is prior intravenous antibiotic therapy within 90 d. Additional risk factors for MDR VAP are septic shock, acute respiratory stress syndrome (ARDS) preceding VAP, ≥5 d of hospitalization prior to VAP and concomitant renal replacement therapy (Kalil *et al.* [166]).

Current guidelines recommend the use of combination therapy in patients with risk factors for multiresistant pathogens, sepsis-associated organ dysfunction, and invasive ventilation, respectively. Combination therapy should be re-evaluated after 72 h at the latest. The rationale for combination therapy in empirical initial therapy is primarily to broaden the antibacterial spectrum to multiresistant pathogens such as, e. g., MRSA or ESBL-forming pathogens, to ensure an active therapy. In targeted therapy of septic cases synergistically acting bactericidal antibiotics may achieve a fast infection control by rapid pathogen eradication. Additionally, rapid resistance development, for example in *P. aeruginosa*, is thereby avoided (Kalil *et al.* [166], Dahlhoff *et al.* [72]).

Intravenous fosfomycin is well suited for the treatment of HAP/VAP, as its broad antibacterial spectrum covers most of the causative species such as *P. aeruginosa*, including MDR strains, MRSA, and ESBL- or carbapenemase-producing pathogens. In addition, i. v. fosfomycin exhibits rapid bactericidal activity and synergism with all classes of antibiotics (Section 2.4.2). It penetrates readily into infected lung tissue, surpassing the MIC of susceptible pathogens shortly after infusion (Matzi *et al.* [216]).

Table 20: Overview of clinical studies on the use of fosfomycin in HAP/VAP.

First author [Ref.]	Age of pts. (yr)	*N*	Study design	Indication	Therapy regimen	Dose of fosfomycin	Clinical outcome	Microbiological outcome
Bodmann, study ongoing [44]	44–91	919	Prospective	12 pts. with HAP/VAP	Fosfomycin, mostly comb. therapy	12 g/d (range 6–15 g)	Clin. success (incl. microbiol. cure) in 7/12 (88%) of pat. w. nosocomial resp. tract inf.	88% at test-of-cure time
Dinh [82]	adults: Ø 67 (16–98) children: Ø 5 (1 month–15 yr)	101 ad.; 15 ch.;	Prospective	33 pts. with lung inf. incl. 17 nosocomial inf. on mechanical ventilation	Fosfomycin comb. therapy	12–16 g/d (4 g every 8 or 6 h)	21/31 (67%) fav. outcome, 10 unfav. clin. outcome (32.3%) and two died (6.5%)	79.5% (66/83) in monobacterial inf. (all ind.)
Khawcharoenporn [177]	70–83	84	Retrospective	XDR *P. aeruginosa* pneumonia	Fosfomycin comb. therapy	4 g every 8 h	Clin. cure: Gr. 1: 17/18 (94.4%) Gr. 2: 15/17 (88.2%); not significant	Microbiol. cure: Gr. 1: 5/10 (50%) Gr. 2: 5/9 (55.5%); not sign.
Nissen [243]	Gr. 1: Ø 56.9 Gr. 2: Ø 57.8	32	Prospective, randomised	Severe pneumonia (ventilator-associated in 22 pts.)	Gr. 1 (*n* = 17): Fosfomycin plus ampicillin Gr. 2 (*n* = 15): Gentamicin plus ampicillin	4 g every 8 h (12 g/d)	Gr. 1 (fosfomycin + ampicillin): 58.8% complete success, 35.3% partial success, 5.9% failure. Gr. 2 (gentamicin + ampicillin): 46.7% complete success, 33.3% partial success, 20% failure.	Gr. 1: 87.5% success rate Gr. 2: 90% success rate
Pontikis [267]	56.7 ± 17.2	48	Prospective	14 pts. with VAP	Fosfomycin comb. therapy	median dose of 24 g/d (IQR 16–24 g/d)	10/14 (71.4%) success; 3/14 treatment failure (21.4%) 1/14 superinfection (7.1%)	6/14 (43%) eradication, 5/14 (36%) persistence, 3/14 (21%) indeterminate

First author [Ref.]	Age of pts. (yr)	*N*	Study design	Indication	Therapy regimen	Dose of fosfomycin	Clinical outcome	Microbiological outcome
Putensen [272]	mean 59 (ITT)	209	Prospective	Miscellaneous, 27 pts. with HAP, VAP or CAP	Fosfomycin in comb. with carbapenems (60%), glycopeptides (28%) cephalosporins (24%), colistin (20%), quinolones (16%)	23/27 ≤15 g/d, 4/27 >15 g/d	Clin. success 23/27 (85.2%, cPP)	53.8% eradication (7/13, mPP))
Wenisch [347]	62.4 ± 16	29	Prospective	VAP	Fosfomycin in comb. with cefpirome	8 g every 12 h	Clin. success 65.5% (19/29)	NR

cPP: clinical per protocol population; mPP: microbiological per protocol population; IQR: Interquartile range; ITT: Intention to treat; NR: Not reported.

Core data of studies collecting clinical data of fosfomycin efficacy as part of an antibiotic combination regimen are listed in Table 20. Fosfomycin was studied in combination therapy in two prospective clinical studies encompassing patients with severe pneumonia (Nissen *et al.* [243], Wenisch *et al.* [347]): Nissen *et al.* included 32 patients with severe acute pneumonia treated either with i. v. fosfomycin (3× 4 g/d) plus ampicillin (4× 1 g/d) or with gentamicin (3× 80 mg/d) plus ampicillin. Both treatment groups showed no significant differences with a trend towards better outcomes in the group treated with fosfomycin combinations (Nissen *et al.* [243]). Wenisch and colleagues studied combination therapy using fosfomycin (2× 8 g/d) with cefpirom (2× 2 g/d) in septic patients with ventilator-associated pneumonia. Complete success was achieved in 19/29 (65.5%) patients. The authors concluded that cefpirome combined with fosfomycin is an effective and safe treatment for septic patients with ventilator-associated pneumonia (Wenisch *et al.* [347]).

Pontikis *et al.* studied the outcomes of critically ill patients treated with fosfomycin in combination with various other antibiotics for infections caused by pan-drug or extensively drug-resistant gram-negative species and reported clinical success rates of 80% (8/10) in patients with ventilator-associated pneumonia even in the subgroup of patients with a generally unfavourable prognosis (Pontikis *et al.* [267]). Likewise, another prospective study on the efficacy of fosfomycin against infections caused by multidrug-resistant bacteria reported favourable outcomes in 67% (21/33) of patients with lung infections treated with fosfomycin in combination with other antibiotics (Dinh *et al.* [82]).

Khawcharoenporn *et al.* performed a retrospective cohort study in adult patients with extensively drug resistant (XDR) *P. aeruginosa* HAP/VAP. All XDR-PA isolates were susceptible only to colistin and/or fosfomycin. Definite treatment regimens were categorised into 3 groups: 1) inactive therapy; 2) active monotherapy and 3) active combined two-drug therapy. Outcomes were compared between the 3 groups. A total of 136 patients were included

(37% VAP). In group 3, 36/40 patients received fosfomycin combination therapy. Rates of 28-day survival and microbiological cure were significantly higher in group 3 as compared to groups 2 and 1 (90% vs. 51% vs. 0%; $p < 0.001$ and 90% vs. 54% vs. 0%; $p < 0.001$, respectively) (Khawcharoenporn *et al.* [177]).

In the recent NIS-FOM study, 32/209 (15.3%) patients with community-/hospital-acquired or ventilator-associated pneumonia (CAP, HAP, VAP) were included. The overall clinical success in this subgroup was notably high (23/27 cPP, 85.2%) (Putensen *et al.* [272]).

A first provisional subgroup analysis of the still ongoing prospective, multinational, multicentre and non-interventional FORTRESS study included 12/124 patients from 10 German study centres with HAP or VAP. Clinical success (including microbiological cure), defined as clinical cure or improvement at the end of fosfomycin treatment, was achieved in 7/8 (88%) patients (Bodmann *et al.* [44], study ongoing).

The German S2k guideline for the empirical antibiotic treatment of bacterial infections recommends fosfomycin as a combination partner for the first-line treatment of nosocomial pneumonia in high-risk patients (e. g., extra-pulmonary organ failure, severe respiratory insufficiency, antimicrobial pre-treatment, etc.). Fosfomycin should be administered in a dosage of 5–8 g fosfomycin i. v. three times a day in combination with an antipseudomonal broad-spectrum β-lactam antibiotic (Bodmann *et al.* [43]).

3.6 Complicated skin and soft-tissue infections

- Fosfomycin tissue penetration is not negatively affected by inflammation or sepsis.
- Fosfomycin is well suited for severe, septic, or phlegmonous cSSTI.
- This also prevails when other difficult-to-reach compartments (such as abscesses, bone tissue) are involved.

Skin and soft-tissue infections (SSTIs) encompass a variety of pathological conditions and may involve – depending on the severity and the origin of the infection – the skin and the underlying subcutaneous tissue, fascia or muscle and may range from non-severe superficial to potentially life-threatening and disabling necrotising infections with high mortality. The origin of an SSTI may derive from small superficial lesions, chronic and surgical wounds, or acute trauma. Internationally, no unique, generally accepted definitions for skin and soft-tissue infections exist, but a classification as either uncomplicated or complicated is useful in describing skin and soft-tissue infections. According to common definitions (US, EU), cSSTI include, e. g., deep-seated infections, surgical or wound site infections, major abscesses, infected ulcers or burns, infective cellulitis, the requirement of surgical intervention, the presence of sepsis or other complicating co-morbidities, or accompanying tissue necrosis (Sartelli *et al.* [294], Burnham *et al.* [54], Stevens *et al.* [316], US FDA [334], Bodmann *et al.* [43], Leong *et al.* [192]).

Recently, i. v. fosfomycin has become licensed for the treatment of patients with cSSTI across Europe (European Medicines Agency [92]). cSSTIs have been described as an important focus for severe sepsis or septic shock following pneumonia and abdominal infections (Sartelli *et al.* [294]). This indication adequately describes the present clinical use of fosfomycin for the treatment of severe SSTIs such as necrotising fasciitis and myositis, post-traumatic and post-operative soft-tissue infections, diabetic foot infections, and wound infections, in

particular with abscess involvement in critically ill patients in intensive care. In these indications, i. v. fosfomycin is used in combination therapy.

As described in Sections 2.4.1.4 and 2.4.1.5, fosfomycin penetrates well in subcutaneous tissue, skeletal muscle, and adipose tissue. After commonly employed clinical doses of 4 to 8 g i. v. fosfomycin, appropriate target-site concentrations are reached that are able to eradicate relevant pathogens such as gram-positive cocci and gram-negative bacilli, including MDR strains, which may be involved in skin and soft-tissue infections in critically ill patients (Legat *et al.* [191], Joukhadar *et al.* [161], Frossard *et al.* [112], Dorn *et al.* [84], Schintler *et al.* [297], Zeitlinger *et al.* [357]).

Importantly, the tissue penetration of fosfomycin was shown to be unaffected by inflammation and sepsis (Legat *et al.* [191], Joukhadar *et al.* [161]). This finding is of particular relevance as previous studies have shown that the equilibration process between plasma and tissue interstitium may be prolonged or even be incomplete for several other antibiotics such as β-lactams or glycopeptides in intensive-care patients (Joukhadar *et al.* [160], Brunner *et al.* [53], Tegeder *et al.* [324], Abraham *et al.* [2]).

Percutaneous and surgical abscess drainage is not always successful or possible for source control in each case, and the use of systemic antibiotics after incision and drainage has been demonstrated to result in increased rate of clinical cure (Gottlieb *et al.* [124]). As major cutaneous abscesses are often found in cSSTIs and are the main symptoms for certain diseases (e. g., pyomyositis), it is important to understand whether antibiotics are able to penetrate these compartments as well. Abscesses can constitute a high risk of complications and belong to the type of compartments that are generally difficult to reach with antibiotics. Sauermann and colleagues showed that fosfomycin concentrations in the purulent fluids from various abscesses, including skin and soft-tissue abscesses, after multiple fosfomycin doses at steady state (maintenance dose of 8 g every 8 hours) reached a median concentration of 178 mg/L with a long median half-life of 21.8 hours. The fosfomycin concentrations exceeded the MIC50/90 of bacterial species that are commonly involved in abscess formation, such as staphylococci, streptococci, and *Escherichia coli* (Sauermann *et al.* [295]).

Necrotising skin and soft-tissue infections are rare but aggressive diseases, frequently accompanied by sepsis or septic shock, and with a high mortality. Clinical evidence on the optimal antibiotic treatment is, in general, limited, but it seems obvious that a broad-spectrum, bactericidal antimicrobial therapy needs to be initiated without any delay upon diagnosis (Peetermans *et al.* [257]). A large body of data on the use of fosfomycin in combination with other antibiotics in adults and children presenting with life-threatening necrotising fasciitis due to multiresistant *Pseudomonas aeruginosa*, staphylococci, and enterobacteria are available in the literature (Waiwarawooth [343], Fustes-Morales *et al.* [114], Häusler *et al.* [143], Hashimoto *et al.* [142], Hirk *et al.* [148], Kluge *et al.* [179]). For example, Maier and colleagues reported about two cases of life-threatening, necrotising soft-tissue infection in which the combination of fosfomycin and meropenem combined with rapid surgical debridement, intensive care, and hyperbaric oxygenation proved to be an effective antimicrobial therapy (Maier *et al.* [207])

Post-traumatic and post-operative soft-tissue infections often represent challenging infections, complicated by the presence of polymicrobial or MDR pathogens. In post-traumatic and post-operative soft-tissue infections, a combination therapy with fosfomycin (8 g twice daily or adjusted to renal clearance) plus clindamycin, rifampicin, cefazolin or isoxazolyl penicillins for at least 6 days was successfully studied. In a study by Wildling *et al.*, patients

were allocated to three groups according to the site of infection (Wildling *et al.* [350]). All patients were treated with fosfomycin as a follow-up therapy after unsuccessful initial antibiotic treatment. Group 1 included 28 patients (age range 17–81 yr) suffering from post-operative soft-tissue infections (14 pts. after heart and vascular surgery, 10 pts. with intra-abdominal surgery, and 2 pts. after jaw surgery) caused by staphylococci, enterococci or mixed flora. In this group, 24 patients were cured, one patient improved, and four patients died from fungal infection or cardiac decompensation. The two patients who received fosfomycin as monotherapy (8 g twice daily for seven days) were also cured. Group 2 consisted of 14 patients (age range 17–78 yr) with various soft-tissue infections, mainly accompanied by osteomyelitis of the adjacent bones. 10 of these patients suffered from acute exacerbations of chronic osteomyelitis. The treatment duration with fosfomycin-containing antibiotic combinations was 7–20 days. Four patients were cured after 7–12 days, one patient after 20 days. The remaining nine patients were classified as markedly improved. The antibiotics co-administered with fosfomycin included β-lactams, aminoglycosides, rifampicin, and clindamycin. Group 3 consisted of 11 patients (age range 16–84 yr) with post-traumatic infectious complications such as abscesses, meningitis, and empyema caused by staphylococci and various gram-negative bacteria. With a combination of fosfomycin plus β-lactams or clindamycin for 7 to 30 days, seven patients were cured and three improved. One patient deceased from aspiration pneumonia. In the overall study, all patients with sepsis (n = 8) were cured (Wildling *et al.* [350]).

Putensen *et al.* described the present use of i. v. fosfomycin under real-life conditions in 209 patients (Putensen *et al.* [272]). 7% of patients (14/209) who received i. v. fosfomycin suffered from infections of the skin and soft tissues. The majority of SSTI were polybacterial (9/12), 4 additionally due to a MDR pathogen (33%), and another 4 with fungal involvement (33%). Clinical success, defined as either as clinical cure or clinical improvement, was achieved in 10/12 (83.3%) of these patients. It is noteworthy that despite the complex microbiological situation due to polybacterial infections with MDR and/or fungi involvement, eradication was achieved in all patients with evaluable microbiological endpoint (8/8) (Putensen *et al.* [272]).

Use of i. v. fosfomycin in patients with severe infections including cSSTI under real-life conditions is currently studied in the ongoing international FORTRESS study (Bodmann *et al.* [44]). A recently published interim analysis showed that 24 of 245 currently (01/2020) enrolled patients with severe infections had cSSTI (11 female, 13 male; mean age 58 yr), of which 17 (71%) were treated in intensive care. 14 (58%) patients had at least one additional risk factor for cSSTI, e. g., diabetes mellitus, immunosuppression, hepatic cirrhosis, drug (hepatitis B/C) or alcohol abuse. 10 (42%) patients had sepsis or septic shock at baseline. Fourteen patients (58%) had surgical site infections, 18 (75%) non-necrotising cSSTI, thereof 14 (78%) with abscess formation, and 4 (17%) necrotising cSSTI (fasciitis, cellulitis/severe phlegmon, burn wound infection, abscess). 20 cases (83%) of cSSTI were considered as acute, and 4 (17%) as chronic infections. Surgery associated to cSSTI, e. g. debridement, drainage or device removal/implantation, was required in 18 patients (75%). 18 (75%) infections were microbiologically confirmed. Causative pathogens were mostly staphylococci (15/38 isolates; 39%), particularly methicillin-sensitive *S. aureus* (n = 10/38 isolates; 26%), *E. faecium* (1/38 isolates; 3%), *Streptococcus* spp. (n = 5/38 isolates; 13%), and gram-negative species (n = 12/38 isolates; 32%). Intravenous fosfomycin was used in a dose of 14 g/d (median) for a mean duration of 20 days, often in combination with penicillins, cephalosporins or carbapenems. Clinical success was reported in 19/24 (79%) patients, in 12/15 (80%) patients with abscess involvement, and in 8/10 (80%) patients with concomitant sepsis or septic shock. Patients receiving a daily fosfomycin dose of 15 g or

more seemed to have a better clinical outcome compared to those receiving less than 15 g, with clinical success rates at end of fosfomycin treatment of 83% (10/12) and 75% (9/12), respectively. 15 patients had adverse drug reactions (14 non-serious: hypernatraemia (*n* = 6), hypokalaemia (*n* = 4), hyperkalaemia (*n* = 1), nausea (*n* = 1), vomiting (*n* = 1), and diplopia (*n* = 1); 1 serious: hypokalaemia) (Kluge *et al.* [179]).

Intravenous fosfomycin as combination partner in a dosage of 12–24 g is therefore well-suited for treatment of cSSTIs. This conclusion is supported by its excellent penetration in the interstitial fluid of soft tissues (adipose tissue, skeletal muscle) and abscesses and the fact that its antibacterial spectrum covers relevant gram-positive cocci and gram-negative bacilli. The S2k guideline of the German Paul-Ehrlich-Society for Chemotherapy recommends fosfomycin combinations for the treatment of severe phlegmon or as a second-line option in cSSTI caused by MRSA (Bodmann *et al.* [43]).

3.7 Bacterial meningitis

- Intravenous fosfomycin shows excellent penetration into the CNS, acts bactericidal against relevant pathogens, and is therefore recommended for the treatment of bacterial meningitis and brain abscesses
- These infections are treated with higher doses of i. v. fosfomycin (16–24 g/d in 3–4 individual doses)

Bacterial central nervous system (CNS) infections, such as meningitis, encephalitis, ventriculitis, and brain abscesses, are rare but potentially life-threatening infections with high morbidities and mortalities. For this reason, they require prompt recognition and treatment (Dorsett *et al.* [85], O'Horo *et al.* [249]).

Fosfomycin is indicated for the treatment of bacterial meningitis (including brain abscess), which is defined as a severe infectious disease of the membranes lining the brain, often characterised by accompanying abscess formation. Primary or community-acquired bacterial meningitis occurs in all age groups, but is nowadays, due to the introduction of paediatric vaccination, more prevalent in adults, including immunocompromised patients (Van de Beek et al [337]). In contrast to post-traumatic and hospital-acquired forms of meningitis (i. e., forms associated with traumatic head injuries, craniotomy and cranioplasty, neurosurgery for neurosurgical implants such as CSF shunts or external lumbar or ventricular CSF drainages or for other spinal procedures) that are typically caused by pathogens such as *S. aureus*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* (Conen *et al.* [64]), the primary or community-acquired bacterial meningitis is commonly associated with pathogens such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Brain abscesses may arise as complication of the epidural or subdural meningitis, particularly after traumatic brain injuries or neurosurgical interventions or *de novo* from haematologous seeding.

Since the brain is an immunoprivileged site and the blood/brain barrier drastically reduces the diffusion of antimicrobials in the CNS, it is of utmost importance to investigate whether antibiotics can penetrate into the CNS to achieve effective concentrations and prefer antibiotics with bactericidal activity (Nau *et al.* [236], Tattevin *et al.* [323], Forrester *et al.* [108]). CNS infections with limited or no meningeal inflammation such as ventriculitis or brain abscess can result in even lower CNS penetration of antibiotics. These limitations make antibiotic therapeutic options quite limited for the treatment of CNS infections. Despite

limitations such as poor diffusion rate into CSF at baseline (<15%) and their hydrophilic properties, selected β-lactams represent the backbone of most antibacterial treatment regimens for CNS infections (Pfister [264], Van de Beek *et al.* [337], Tattevin *et al.* [323].

Standard antibiotics such as third- or fourth-generation cephalosporins, meropenem, flucloxacillin, or vancomycin are less CNS-permeable as intravenous fosfomycin. It is therefore often doubtful if therapeutically effective drug levels can be reached in the CNS, especially if these antibiotics are used in monotherapy (Blassmann *et al.*,[42]). Linezolid with its bacteriostatic activity might be an unsuitable therapeutic option despite its good CNS penetration, especially in critically ill patients with reduced immune response (Ntziora *et al.* [245])). Daptomycin is bactericidal, but does not cross the blood/brain barrier, which makes it ineffective for the treatment of CNS infections (Kullar *et al.* [185]). Hence, CNS infections represent excellent examples for difficult-to-treat infections that are not yet adequately addressed by standard therapy. This problem is further aggravated by the pharmacokinetic hurdle due to the blood/brain barrier.

Fosfomycin is well suited for the treatment of infections of the CNS, because it is effective against the most relevant pathogens, it exhibits synergy with other antibiotics used in this indication, it is active against biofilms, and it penetrates easily across the blood/brain barrier in both healthy and inflamed meninges (Tsegka *et al.* [332], Table 7) This ensures that in bacterial meningitis and brain abscesses, the concentrations necessary for the reliable eradication of bacterial pathogens are maintained in the CSF for an adequate period (Friedrich *et al.* [111], Pfeifer *et al.* [263], Pfausler *et al.* [262], Oellers *et al.* [248]).

The published evidence regarding effectivity and safety for intravenous fosfomycin in the treatment of patients with CNS infections was summarised by Tsegka *et al.* Data from 32 publications with 224 paediatric and adult patients were analysed in this current literature review. Details on i. v. fosfomycin treatment, indications, and clinical and microbiological outcomes are shown in Table 21. Combination treatment was used in 87% of all patients. *Staphylococcus* spp. including MRSA and MRSE were the most prominent isolates found, followed by *Streptococcus pneumonia*, *Neisseria meningitides* and several other pathogens including MDR and XDR pathogens. The most commonly used dose of i. v. fosfomycin was 14–16 g per day, with a maximum of 24 g per day. Data from this comprehensive review of the available evidence show that intravenous fosfomycin is an effective and well-tolerated combination partner for the treatment of bacterial meningitis, including brain abscess of various origins (Tsegka *et al.* [332]).

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) also recommends fosfomycin as a combination partner for the treatment of bacterial meningitis caused by MSSA and MRSA (Van de Beek *et al.* [337]). The current German recommendation for the targeted antibiotic treatment of bacterial infections lists fosfomycin as a combination partner for the first-line treatment of bacterial meningitis caused by *P. aeruginosa*, MSSA and MRSA (Bodmann *et al.* [43], Pfister *et al.* [264) and for the empirical treatment of community-acquired brain abscesses (Nau [238]). The management of neurosurgical implant-associated infections, including the possible role of i. v. fosfomycin, was reviewed by Conen and colleagues (Conen *et al.* [64]).

The use of i. v. fosfomycin in the indication bacterial meningitis is thus strongly supported by the available clinical evidence when combined with other antibiotics because of its ability to cross the blood/brain barrier in healthy and inflamed meninges and to concentrate in the cerebrospinal fluid, particularly in the case of meningeal inflammation up to threefold compared to non-inflamed meninges. Fosfomycin achieves high concentrations above the clinical breakpoints of susceptible species, is synergistic with other antibiotics used to treat

Table 21: Data on the use of fosfomycin as first- or second-line treatment, combination treatment or monotherapy, the types of CNS infections treated and the clinical and microbiological outcome.

	Number of patients	Portion (%)
First/second line treatment		
Fosfomycin as first line treatment	164	73.3
Fosfomycin as second line treatment	15	6.7
Not specified	45	20
Combination treatment	195	87
Monotherapy	29	13
Type of CNS infection		
Meningitis	123	54.9
Brain abscess	33	14.7
Spinal abscess	6	2.7
Ventricle empyema	3	1.3
CSF shunt infection	12	5.4
Not specified/other	47	21
Clinical outcome		
Cure	184	88.5
Cure with neurological sequelae	11	5.3
Death	13	6.2
Microbiological outcome		
Sterilization of CSF	138	97.2
Failure of sterilization of CSF	2	1.4
Sterilization of blood cultures	1	0.7
Post- mortem growth of *Mycobacterium tuberculosis complex*	1	0.7

Abbreviations: CSF: cerebrospinal fluid, CNS: central nervous system

CNS infections, and exhibits antibacterial activity against pathogens relevant in bacterial meningitis or brain abscesses.

3.8 Complicated intra-abdominal infections

- Intravenous fosfomycin penetrates readily in intra-abdominal fluids and organs.
- Intravenous fosfomycin is a valuable option as companion drug for abdominal infections with abscess formation and/or caused by multiresistant pathogens.

Intra-abdominal infections (IAIs) are common, comprise a wide heterogeneity of clinical conditions, and are divided into uncomplicated and complicated conditions (Sartelli *et al.* [292, 293]). By definition, in contrast to uncomplicated intra-abdominal infections, in which the infection only involves a single organ, the infectious process in complicated intra-abdominal

infection (cIAI) moves beyond the affected organ and causes either localised or diffuse peritonitis or abscess(es). Complicated intra-abdominal infections are a major cause of sepsis and septic shock and are an important cause of morbidity and mortality. In a recent prospective international multicentre study in patients with cIAI from various origins, the overall mortality was reported as 9.2% across all single clinical entities (Sartelli *et al.* [291]). The treatment of patients with cIAI requires early diagnosis and adequate surgical infectious source control combined with an adequate antimicrobial therapy. Important criteria for the adequate selection of an appropriate antibiotic therapy are the clinical condition of the patient (prior treatment, immunosuppression), the expected pathogen spectrum with individual risk for infection by resistant pathogens, local pathogen and resistance data, and a low toxicity of the antibiotic, in particular for the treatment of critically ill patients. Especially in this latter vulnerable patient population, an adequate antimicrobial therapy is challenged by multidrug-resistant infections caused by gram-positive and gram-negative pathogens and by the limited clinical evidence from RCTs for all antibiotics commonly used for treatment, as these patients are usually excluded from enrolment into studies. Additionally, IAIs are often polymicrobial in nature (Putensen *et al.* [272]). Therefore, the selection of one preferred antibiotic or treatment regimen for the treatment of these critically ill patients with cIAI is not possible. A broad-spectrum antibiotic therapy that includes a combination of different antibiotic classes is recommended in patients with previous antibiotic administration, in settings with high rates of MDR pathogens, and in patients with septic shock (Sartelli *et al.* [293]).

Intravenous fosfomycin is a broad-spectrum antibiotic active against many gram-negative and gram positive pathogens, including MDR isolates, that are commonly found in patients with cIAIs. It is of note that certain gram-positive anaerobes from the gut flora are also susceptible to fosfomycin (*Peptococcus* spp., *Peptostreptococcus* spp.), but gram-negative anaerobic bacteria such as *B. fragilis* are not covered by the antibacterial spectrum of fosfomycin. Intravenous fosfomycin exhibits a good penetration into intra-abdominal fluids or organs (e. g., peritoneal fluid, bile and gallbladder, appendix) and intra-abdominal abscesses, which are frequent and often the location of surgically intractable intra-abdominal infections (Sauermann *et al.* [295], Nakamura *et al.* [234], Bando *et al.* [25]). Therefore, i. v. fosfomycin is an attractive candidate for the empirical therapy in the management of secondary or tertiary intra-abdominal infections, in particular in patients with sepsis or septic shock (Bodmann *et al.* [43]). Timely and effective antimicrobial therapy is one of the most important variables associated with a favourable outcome in these critically ill patients (Sartelli *et al.* [293]).

Kusachi et al. studied the effects of fosfomycin combination therapy in 104 patients with refractory intra-abdominal abscesses, where drainage combined with initial antibiotic treatment had been unsuccessful in all cases (Kusachi *et al.* [188]). Despite the complicated nature of the underlying infection, fosfomycin showed a remarkable high efficacy rate of 87.5% (91/104). Interestingly, administration of the combination partner – mostly carbapenems – was started one hour after infusion completion of i. v. fosfomycin in a time-lag fashion, based on the assumption that fosfomycin can break up biofilms and therefore enhance the permeability of the combination partner. The authors conclude that this treatment approach is effective for the treatment of patients with intra-abdominal abscesses where prior drainage using various surgical techniques was unsuccessful, with ongoing systemic signs of infection, and where further source control would be too invasive for relatively small abscesses and not feasible due to the risk of injury to organs.

Already published in 1987, Andåker and colleagues showed the successful prophylactic use of i. v. fosfomycin in combination with metronidazole for the prevention of septic complications after emergency abdominal surgery (Andåker *et al.* [14]). In this prospective, randomised study, the authors administered pre-operatively (intravenously 1 h before surgery) either 160 mg gentamicin plus 0.5 g metronidazole, or 4 g fosfomycin plus 0.5 g metronidazole in 381 patients with acute abdominal disorders requiring emergency surgery. The patients were further stratified for the underlying diagnosis in three treatment groups that determined whether the patient received 0, 3, or 4 additional doses during the post-operative period. In diagnosis groups A (acute appendicitis) and B (gangrenous appendicitis, intra-abdominal disorders with minor contamination), the incidence of septic complications did not differ significantly between the infection prevention regimens. In diagnosis group C (peritonitis, perforated gastroduodenal ulcer, intestinal perforation of any kind), septic complications occurred more frequently after gentamicin/metronidazole treatment (14.9% versus 2.0%, $p < 0.05$). Among all 84 patients with peritonitis, the sepsis rate was higher for the gentamicin/metronidazole study group than for fosfomycin/metronidazole-treated patients (13.2% versus 2.2%, $p < 0.13$). No untoward effects were observed for any regimen (Andåker *et al.* [14]).

Recent clinical data have shown the successful clinical use of i. v. fosfomycin in patients with cIAI both caused by non-MDR and MDR pathogens from different aetiologies in real life settings. Dinh *et al.* reported on 7 patients with intra-abdominal infections in their prospectively performed cohort study with 116 patients from France. MRSA, methicillin-resistant coagulase-negative staphylococci or *Enterococcus* spp. were isolated in 5 cases. *P. aeruginosa*, *E. coli*, *Klebsiella*/*Enterobacter*/*Serratia* were isolated in another 5 cases, suggesting that IAI infections were partially polybacterial. A favourable outcome was reported in 4/7 (57%) patients, failure in 2/7 (29%), and an insufficient follow-up in 1/7 (14%) (Dinh *et al.* [82]).

Pontikis *et al.* included 7 patients with intra-abdominal infections in their prospective case series of 48 patients from Greece suitable for effectiveness analysis, all of them with involvement of pan-drug-resistant or XDR carbapenemase-producing gram-negative bacteria. Of these 7 patients, one suffered from ischaemic colitis, three from tertiary peritonitis, one from complicated pancreatitis and two from intra-abdominal abscess. All patients received surgical treatment. Secondary bacteraemia was detected in 4 patients. Clinical success was reported in 3/6 patients with evaluable clinical endpoint (50%), failure in 2/6 patients (33.3%) and an indeterminate outcome in 1/6 patients (16.7%) (Pontikis *et al.* [267]).

Another recent prospective cohort study with 209 patients from Austria and Germany included 23 patients with IAI, 22 of which had an evaluable clinical and 10 an evaluable microbiological endpoint. The clinical success was 72.7% (16/22) and the microbiological success 30% (3/10). 9 patients had a polymicrobial infection and 21/22 patients presented with relevant co-morbidities such as concomitant oncologic diseases or immunosuppression/HIV. Arterial hypertension, chronic renal insufficiency, CHD, and obesity (BMI > 30 kg/m^2) were represented in these patients as well as known risk factors for infections such as smoking, diabetes mellitus, and liver cirrhosis (Putensen *et al.* [272]).

Treatment of intra-abdominal infections (cIAI) with i. v. fosfomycin is recommended by the German Paul-Ehrlich-Society for Chemotherapy. Here, combination therapy with fosfomycin is endorsed for the treatment of nosocomial (post-operative/tertiary) peritonitis due to *Enterobacteriaceae* (incl. ESBL-producers), enterococci (incl. VRE), anaerobes, *Pseudomonas* spp., and staphylococci (incl. MRSA) with daily fosfomycin dosages of 3× 4–8 g. In particular for the treatment of IAI with high risk of involvement of ESBL-producers (*E. coli*, *Klebsiella* spp.), i. v. fosfomycin is recommended as the treatment option of choice (Bodmann *et al.* [43]).

Furthermore, in the consensus statement from the Austrian Society of Infectious Diseases and Tropical Medicine (OEGIT), i. v. fosfomycin is recommended as treatment option in nosocomial post-operative or tertiary abdominal infections with abscess involvement (such as anastomosis insufficiency or recurrent infections after surgical sanitation) (Thalhammer *et al.* [326]).

In two expert papers from Italian authors, i. v. fosfomycin is recommended as a companion drug for the treatment of IAI caused by carbapenem-resistant *Klebsiella penumoniae*. Petrosillo *et al.* recommend i. v. fosfomycin in abdominal infections due to colistin-resistant and serine carbapenemase-producing (i. e., KPC, OXA-48 like) *Klebsiella pneumoniae* with a meropenem MIC > 16 mg/L as a combination partner of a backbone regimen consisting of ceftazidime/avibactam and tigecycline (Petrosillo *et al.* [261]). Likewise, in an expert opinion by Bassetti *et al.,* i. v. fosfomycin is recommended as a companion drug for intra-abdominal infections due to KPC-producing *K. pneumoniae* with meropenem MICs ≤ 8–16 mg/L in a daily dose of 24 g/d (4 g every 4 h) (Bassetti *et al.* [34]).

From a clinical and pharmacological perspective, i. v. fosfomycin is well suited for the combination therapy of complicated IAI, as it penetrates readily into fluid abscesses which are frequent locations of intra-abdominal infections (which makes it especially useful for the treatment of surgically intractable intra-abdominal abscesses) or into other intra-abdominal fluids or organs (e. g., peritoneal fluid, bile and gallbladder or appendix) and exhibits sufficient antibacterial activity against relevant pathogens.

3.9 Bacteraemia and sepsis

- Intravenous fosfomycin is suitable for the empiric and targeted treatment of sepsis.
- Recent data suggest that i. v. fosfomycin combination therapy achieves better clinical outcomes in SAB patients at high risk of complications or relapse than monotherapy without fosfomycin.

Bacteraemia may arise secondarily to a localised infection at a specific body site or may be classified as primary when no focus is identified. If an infection is accompanied by a life-threatening organ failure due to a dysregulated immune response, the current Sepsis-3 definition of a sepsis is met. An additional compromised haemodynamic situation with mandatory vasopressor treatment and elevated lactate defines the condition of septic shock (Singer *et al.* [309], Seymour *et al.* [300], Shankar-Hari *et al.* [301]).

Sepsis and septic shock are major causes of morbidity and mortality worldwide, but are difficult to quantify on an international scale due to major differences in healthcare systems. With these restrictions in mind, an average severe-sepsis lethality of 28% is reported (Fleischmann *et al.* [105]). In 2013, German hospitals reported 279 530 cases of sepsis with 67 849 related deaths (24.8%) to the national reimbursement system (InEK). Lethality increases substantially to about 60% if multiple organ failure or septic shock is involved (Fleischmann *et al.* [106]). These data consign sepsis place three among the most frequent causes of death in Germany.

Depending on the origin of infection, *Staphylococcus* spp., *Streptococcus* ssp. and *Enterococcus* spp. are the most common causes of gram-positive bacteraemia. Among gram-negative bacteria, *Enterobacterales* (*Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis*) and *Pseudomonas aeruginosa* are often responsible for bacteraemia (Bodmann *et al.* [43]).

Multidrug-resistant bacteria are a major concern because a failure of the first antibiotic used increases mortality rates to about 38% (Kang *et al.* [167]). Current guidelines of the Surviving Sepsis Campaign therefore recommend immediate begin of sepsis treatment with one or two broad-spectrum antibiotics to cover all likely pathogens (Levy *et al.* [194]). Combination therapy should be de-escalated if a causative pathogen is found or after 72 h, if the patient improves significantly despite lacking identification of a pathogen (Brunkhorst *et al.* [52]). Furthermore, source control via surgery is mandatory to remove the cause of bacteraemia. This may be difficult in the case of a sepsis of unknown origin as well as in cases where multiple sources (e. g., micro-abscesses) or very instable patients are involved. Additionally, a septic shock may reduce tissue levels of many antibiotics (Joukhadar et al. [160]).

Fosfomycin is well suited for the treatment of severe bacteraemia and sepsis due to its bactericidal activity against the majority of clinically relevant pathogens such as staphylococci and *Enterobacteriales* including multiresistant isolates, taking into consideration that it reaches high serum and tissue levels even under septic circumstances (Joukhadar *et al.* [161]).

3.9.1 Fosfomycin for the treatment of sepsis and septic shock

Several studies evaluated the clinical efficacy of fosfomycin in severe bacteraemia and sepsis. In the study performed by Baron et al., 35 patients (aged 13–70 yr) with MSSA sepsis were treated with either fosfomycin/methicillin (or oxacillin) for a mean period of 17 days (n = 17), or with gentamicin/methicillin (or oxacillin) for a mean period of 11 days (n = 18). There was one death in each treatment group. Cure was achieved in 94% (16/17) of patients with fosfomycin/methicillin, and in 78% (14/18) of patients with gentamicin/methicillin. With gentamicin/methicillin, two superinfections with gentamicin-resistant bacteria and one relapse were noted. With fosfomycin/methicillin, no relapses occurred (Baron *et al.* [31]).

Pontikis *et al.* studied the outcomes of critically ill patients treated with fosfomycin in combination with various other antibiotics for infections with pan-drug or extensively drug-resistant gram-negative species and reported clinical success rates of 61.1% (11/18) for primary bacteraemia, despite the fact that this group of patients was faced with generally unfavourable prognoses (Pontikis *et al.* [267]). A similar study of multidrug-resistant bacteria published by Dinh *et al.* reported favourable outcomes of bacteraemia treated with fosfomycin combinations in 4 of 9 patients completing the observation period and 2 of 9 patients with insufficient follow-up data (Dinh *et al.* [82]).To demonstrate the clinical efficacy of fosfomycin in this indication, one retrospective study was presented comparing the efficacy of fosfomycin combination therapy to other antibiotics for the treatment of sepsis caused by carbapenem-resistant *K. pneumonia* (Liao *et al.* [199]). It was concluded that adjunctive fosfomycin therapy appeared to be associated with improved mortality rates. Another study by del Río et al., which was already mentioned in the context of endocarditis, investigated the efficacy of fosfomycin in combination with imipenem as a rescue therapy in a clinical trial including two patients with bacteraemia caused by MRSA. All patients showed negative blood cultures within 72 hours after the first dose (del Río *et al.* [75]). Coronado-Álvarez *et al.* analysed the clinical efficacy of i. v. fosfomycin combinations against a variety of gram-positive cocci and concluded that a combination therapy of daptomycin plus fosfomycin was more effective than vancomycin plus fosfomycin (success rates of 93% vs. 47%, respectively) (Coronado-Álvarez *et al.* [67]). Besides these clinical studies, a case report was found that supports the treatment of bacteraemia with fosfomycin in combination with vancomycin (Linasmita [201]).

In the still ongoing prospective, multinational, multicentre and non-interventional FORTRESS study, 49/91 (54%) patients presented with bacteraemia or sepsis. Clinical success (including microbiological cure), defined as clinical cure or improvement at the end of fosfomycin treatment, was achieved in 28/40 (70%) patients (Bodmann *et al.* [44]). In the NIS-FOM study, 57/209 (27.3%) of patients developed a clinically and microbiologically confirmed sepsis or bacteraemia during the course of infection, of which 53 had an evaluable efficacy endpoint. Clinical success, defined as either clinical cure or clinical improvement, was achieved in 43/53 (79.2%) patients (clinical per-protocol population) presenting with bacteraemia, sepsis, and signs of infection. It is noteworthy that in patients with bacteraemia of unknown origin, the clinical success was even higher (9/10, 90%), emphasising the important role of i. v. fosfomycin as a broad-spectrum antibiotic in empirical treatment (Putensen *et al.* [272]).

Further studies and case reports indicate a good efficacy of fosfomycin in the treatment of sepsis in children, neonates, and infants (Baquero *et al.* [26], Gouyon *et al.* [125], Dinh *et al.* [82], Gullois *et al.* [131]). The promising use of fosfomycin in studies and its role for treatment of neonatal sepsis caused by MDR bacteria was recently reviewed (Li *et al.* [197]).

The available data provide evidence that fosfomycin could be a live-saving drug in treatment of sepsis and septic shock. Therefore, current German guideline recommendations endorse the use of fosfomycin as a combination partner of acylaminopenicillins, cephalosporins, or carbapenems for the empirical treatment of nosocomial sepsis without identified causative pathogen and unknown focus or suspected to be of pulmonary origin (Bodmann *et al.* [43]). Fosfomycin should be administered in a dose of 12–24 g per day dependent on the clinical circumstances. Furthermore, fosfomycin is recommended for targeted treatment of fosfomycin-susceptible *S. aureus* (incl. MRSA), methicillin-sensitive coagulase-negative staphylococci, *P. aeruginosa*, and ESBL-forming *Enterobacterales* as part of a combination therapy at dosages of 4–8 g trice daily. For the treatment of carbapenem-resistant *Enterobacterales*, a combination of colistin plus 3× 8 g fosfomycin per day is proposed, which is in line with international expert recommendations (Bassetti *et al.* [35]).

3.9.2 Fosfomycin for the treatment of *Staphylococcus aureus* bacteraemia (SAB) in patients with implanted devices

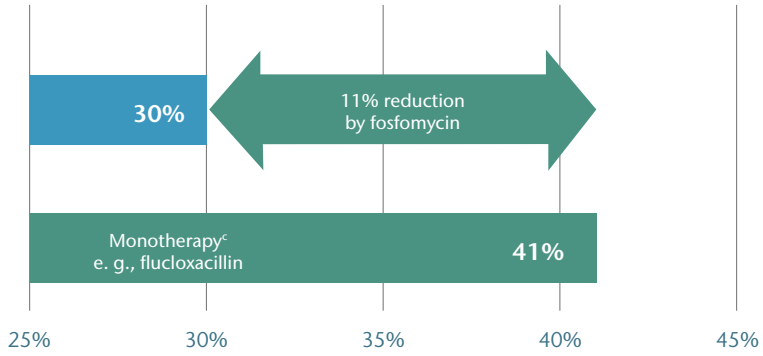
SAB carries a high risk of several complications (e. g., haematogenous dissemination, endocarditis, septic shock, recurrences) with a reported mortality of up to 40–50% despite the fact that the causative pathogen is, in principle, susceptible to standard antibiotic treatment (Kern [176], Tong *et al.* [328]). Hence, the clinical management of SAB differs from that of bacteraemia caused by other pathogens. Uncomplicated SAB needs prolonged intravenous antibiotic therapy over a period of 14 days. A common definition of uncomplicated SAB is given in Box 1. Any other form of SAB is considered a complicated SAB (cSAB) that requires an intensified antibiotic therapy over 4–6 weeks with at least 14 days of intravenous antibiotic treatment (Hagel *et al.* [136], Tong *et al.* [328], Gudiol *et al.* [130]).

Box 1: Criteria for uncomplicated SAB.

- Absence of infective endocarditis
- No implanted foreign bodies
- Negative blood culture after 48 h
- No metastatic dissemination
- Defervescence after 48–72 h of therapy

Combination therapy of cSAB is still a matter of debate (Gudiol *et al.* [130]). According to Thwaites et al., patients receiving combination therapy had a lower risk of recurrence (number needed to treat 29). Patients were randomly assigned to receive 2 weeks of adjunctive rifampicin (600 or 900 mg per day depending on weight, oral or intravenous) vs. identical placebo, together with standard antibiotic therapy. The duration of anti-staphylococcal treatment (29 [IQR 18–45] days) was similar for both groups (Thwaites *et al.* [327]). Recent data from another randomised controlled trail show that the treatment success 6 weeks after end of therapy in patients with MRSA bacteraemia was numerically in favour of the combination of daptomycin and fosfomycin as compared to daptomycin alone (54.1% vs. 42.0%; Pujol *et al.* [271]). Rieg *et al.* recently published a post-hoc analysis of 578 SAB patients at high risk for complications and relapse, e. g., with osteoarticular focus and/or implanted foreign bodies, receiving either monotherapy with an anti-staphylococcal small-spectrum antibiotic (265/578) or a combination therapy with adjunctive fosfomycin (58/313) or rifampicin (255/313). Combination therapy was associated with a lower rate of death or SAB-related late complications within 180 days (HR 0.53, 95% CI 0.35–0.79) and a lower 90-day mortality (HR 0.57, 95% CI 0.36–0.91) with no differences between fosfomycin and rifampicin. The reduction of SAB-related mortality or complications due to fosfomycin combination therapy as compared to anti-staphylococcal monotherapy in patients with osteoarticular infection including foreign bodies is shown in Figure 19 (Rieg *et al.* [278]). It is of note that the use of rifampicin in ICU patients with intensive co-medication is limited because of its high potential for drug interactions due to activation of hepatic CYP enzymes that are involved in the metabolism of a vast majority of drugs.

Reduction of SAB mortality/complications[a] by fosfomycin combination therapy in the treatment of osteoarticular infections incl. device-associated infections[b]



[a]Mortality or 180-d late complications due to *S. aureus* bacteraemia; [b]180-d outcome for SAB with (non-) vertebral osteomyelitis, septic arthritis, or orthopaedic device-associated infection; [c]Flucloxacillin or daptomycin (MSSA) and vancomycin/teicoplanin/daptomycin or linezolid (MRSA), respectively.

Figure 19: Reduced mortality due to fosfomycin combination therapy when compared to anti-staphylococcal monotherapy in patients with osteoarticular infection including foreign bodies (Rieg et al. [278]).

Current Spanish guidelines as well as standard operating procedures in Germany recommend the option of a combination therapy comprising fosfomycin and a high-dose small-spectrum anti-staphylococcal antibiotic for this patient group. Dosing in current guidelines is in line with the Summary of Product Characteristics, recommending a regimen of 4–8 g fosfomycin i. v. trice daily for cSAB treatment (Gudiol *et al.* [130], Hagel *et al.* [137], Bodmann *et al.* [43]). For additional data and recommendations also refer to the sections on endocarditis (Section 3.3) and osteomyelitis (Section 3.4) as well as to Table 22.

Table 22 : Overview of clinical studies on the use of fosfomycin in bacteraemia.

First author [Ref.]	Age range of pts. (yr)	*N*	Study design	Indication	Ther. regimen	Fosfomycin dose	Clinical outcome	Microbiological outcome
Baron [30]	Gr. A: 13–70 Gr. B:13–58	A: 17 B: 18	Prospective	Severe MSSA infections (mostly with septicaemia)	Gr. A: Fosfomycin plus methicillin or oxacillin Gr. B: Methicillin or oxacillin plus gentamicin	Gr. A: Ø 237 mg/kg/d for Ø 17 d Gr. B: –	Gr. A: 16/17 pts. (94.1%) cured, 1 pt. died Gr. B: 14/18 pts. (77.8%) cured (2 pts. had later superinfections, 1 pt. relapsed)	Gr. A: Microbiological cure in 16/17 pts. (94.1%) Gr. B: Microbiological cure in 14/18 pts. (77.8%), 1 pt. relapsed
Bodmann [44] (continued)	30–91	91	Prospective	Miscellaneous; 49 pts. with sepsis/bacteraemia (known, suspected or unknown focus)	Fosfomycin (mostly combined with other antibiotics)	12 g/d (range 6–20 g/d)	28/40 pts. with clinical success (70%); only pts. without involvement of fungi analysed	88% (35/40) microbiological cure
Dinh [82]	101 adults (16–98) 15 children (1 month–15 yr)	116	Prospective	Miscellaneous; 38 pts. with bacteraemia/septic shock, of which 7 with unknown focus	Fosfomycin in combination therapy	4 g 3–4 times a day with variations according to weight and renal failure	57.1% (4/7)	NR
Navarro-San Francisco [239]	54–92	5	Prospective cohort study	Sepsis due to carbapenem-resistant (OXA-48) *K. pneumoniae*	Fosfomycin plus colistin (*n* = 4) or fosfomycin plus tigecycline (*n* = 1)	NR	3 pts. recovered (60%), 2 pts. died from sepsis	NR

First author [Ref.]	Age range of pts. (yr)	*N*	Study design	Indication	Ther. regimen	Fosfomycin dose	Clinical outcome	Microbiological outcome
Pujol [271]	Adults, 74 yr in Gr. D–F	155	RCT	MRSA bacteraemia	Fosfomycin plus daptomycin vs. daptomycin (mono)	2 g q6h	Successful outcome in 40/74 pts. (54.1%) with combination therapy vs. 34/81 pts. (42%) with monotherapy[a]	100% eradication with daptomycin/fosfomycin[b]
Putensen [272]	Mean 59 (ITT)	209	Prospective	Miscellaneous; 53 pts. with bacteraemia/sepsis	Fosfomycin in combination therapy	46/53 ≤15 g/d 7/53 >15 g/d	Clinical success 42/53 (79.2%, cPP)	75.0% eradication (21/28, mPP)
Rieg [278]	Median 67	578	post-hoc analysis of prospective cohort study	"difficult-to-treat" SAB infections	Fosfomycin in combination with small-spectrum anti-staphylococcal antibiotics	3× 5 g/d (adjusted to renal function)	lower rate of death or SAB-related late complications within 180 d in combination group (HR 0.65, 95% CI 0.46–0.92).[c]	n/a

cPP: clinical per protocol population; ITT: Intention to treat; mPP: microbiological per protocol population; RCT: Randomised controlled trial; n/a: Not applicable; NR: Not reported.

[a]Absolute difference 12.1%; CI_{95} = 0–27.0% (numerically much better but not statistically significant); at 7 d after start of therapy successful outcome in 69/74 pts. with combination therapy vs. in 62/81 pts with monotherapy (93.2% vs. 76.5%; absolute difference 16.7%; CI_{95} = 5.4–27.7%, p = 0.008) at ToC visit (0 vs. 9 pts., p = 0.009); [b]Combination therapy was associated with lower rates of microbiological failure than monotherapy; [c]This beneficial effect was primarily seen in patients with implanted foreign devices and orthopaedic devices, in which fosfomycin combination therapy was associated with a lower rate of death or SAB-related late complications within 180 days: Implant orthopaedic device fosfomycin combination therapy group 10/26 (38%) vs. 117/219 (53%) in monotherapy group. Orthopaedic devices 3/11 (27%) in fosfomycin group. vs. 15/36 (42%) in monotherapy group.

Overall, Fosfomycin overcomes several problems associated with other antibiotics such as β-lactams, aminoglycosides, or glycopeptides, as it does not require a therapeutic drug monitoring – even in haemodynamic situations such as sepsis – and does not cause pharmacodynamic drug interactions, making it a particularly suitable combination partner in critically ill septic patients.

4 Clinical safety profile

4 Clinical safety profile

4.1 Summary

- Fosfomycin is well tolerated in all age groups.
- Safety profile was established within 40 years of clinical experience.
- Fosfomycin is an ideal antibiotic for intensive-care patients (no metabolism, no drug/drug interactions, low toxicity).
- No specific safety concerns with higher daily dosages (16–24 g/d).
- Most common side effects are dysgeusia, hypernatraemia, hypokalaemia, erythematous eruption, and injection-site phlebitis, occurring in up to 10% of patients.

4.2 Adverse events

Fosfomycin is well tolerated, and its side effects, if they occur, mostly do not necessitate discontinuation of the treatment (Florent *et al.* [107], Iarikov *et al.* [153]). This is of major importance in infections due to multidrug-resistant pathogens, where intravenous fosfomycin might represent one of the last lines of defence. Clinical studies employing fosfomycin as a part of combination regimens to treat MDR gram-negative infections have not raised safety concerns so far (Bassetti *et al.* [36], Pontikis *et al.* [267], Dinh *et al.* [82]). The predictable and well-investigated safety profile of fosfomycin could also be demonstrated in intensive-care patients, who represent a particularly sensitive population with regards to possible side effects (Putensen *et al.* [272], Pontikis *et al.* [267], Dinh *et al.* [82], Bodmann *et al.* [44], Kluge *et al.* [179], Hagel *et al.* [138]). Even in renal transplant recipients, intravenous fosfomycin was well tolerated with expected adverse events and no cases of graft loss or death (Rosado-Canto *et al.* [281]). In patients with cystic fibrosis receiving colistin and tobramycin or colistin, tobramycin and i. v. fosfomycin, there were no adverse events warranting withdrawal of therapy. The incidence of adverse events was comparable during both treatments (44% vs 50%, respectively; Al-Aloul *et al.* [5]).

After approximately 40 years of using intravenous fosfomycin, reports on severe or serious adverse reactions such as anaphylactic shock and chronic liver toxicity remain anecdotic (Rosales *et al.* [282], Durupt *et al.* [89]). The most common adverse effects of fosfomycin are related to the significant sodium load and include tissue oedema, low serum potassium, headache, vomiting, and taste perturbations. Allergic reactions in the form of skin rashes and angioedema were also described. Moreover, gastrointestinal symptoms (such as taste irritations, nausea, diarrhoea, and pseudomembranous colitis) and leukopenia have been described in the literature. Alkaline phosphatase and transaminase levels may be transiently elevated. Thrombophlebitis and venous intolerance are mostly a result of too rapid i. v. administration (Florent *et al.* [107], Iarikov *et al.* [153], Falagas *et al.* [94], Martindale [213], Roussos et al. [286], Stille [317], Nissen *et al.* [243], Grabein *et al.* [126], Rice *et al.* [277], Putensen *et al.* [272], Kaye *et al.* [175], Matzneller *et al.* [217], Karbysheva *et al.* [171], Pujol *et al.* [271]).

Safety data from the recently conducted ZEUS trial show that intravenous fosfomycin was generally well tolerated. In the safety population (n = 464), treatment-emergent adverse events (TEAEs) were observed in 42.1% and 32.0% of patients in the intravenous fosfomy-

cin and piperacillin/tazobactam groups, respectively. Most TEAEs were mild and transient; premature discontinuation of study drug was uncommon (six patients in the piperacillin/tazobactam group and in 7 patients in the fosfomycin arm).The vast majority of these TEAEs were asymptomatic changes in blood parameters (e. g., elevation in liver enzymes, hypokalaemia) and/or gastrointestinal in nature (e. g., nausea, diarrhoea and/or vomiting). None of the elevations in aminotransferase enzymes were symptomatic and all returned spontaneously to baseline levels after treatment. Hypokalaemia was noted in 30.6% (17.7% mild, 11.2% moderate, and 1.7% severe) of patients treated with fosfomycin versus 12.6% (11.3% mild, 0.9% moderate, and 0.4% severe) of patients in piperacillin/tazobactam. No significant cardiac adverse events were observed. Serious adverse events (SAE) were uncommon (5 in the fosfomycin, 6 in the piperacillin/tazobactam group), with only one drug-related SAE in each study group (hypokalaemia in a fosfomycin patient, renal impairment in a piperacillin/tazobactam patient). No deaths were reported during the study. The study authors considered i. v. fosfomycin an effective and safe treatment option for patients with cUTI and AP (Kaye *et al.* [175]).

A full list of side effects can be found in the Summary of Product Characteristics at the end of this monograph.

High dosage

Dosages between 16 and 24 g/d are commonly considered 'high dose'. In several studies, high fosfomycin single doses of 8 g and daily dosages of up to 24 g/d have been used. Most commonly reported side effects were hypernatraemia, hypokalaemia, transient increase in liver enzymes or gastrointestinal disorders that do not differ from those reported with lower dosages and are known to occur with fosfomycin administration (Pfausler *et al.* [262], Stöckl *et al.* [318], Stengel *et al.* [315], Kaye *et al.* [175], Putensen *et al.* [272], Pontikis *et al.* [267], Matzneller *et al.* [217]; see Summary of Product Characteristics). This suggests that fosfomycin is tolerated even at high doses.

It should be taken into account that maximum daily doses of 24 g are particularly indicated for the treatment of severe infections (see Summary of Product Characteristics). In several expert papers as well as guideline recommendations, high doses of up to 24 g fosfomycin per day are recommended for the treatment of severe life-threatening infections or infections due to multidrug-resistant pathogens (Bassetti *et al.* [33, 34], Tumbarello *et al.* [333], Karaiskos *et al.* [170], Petrosillo *et al.* [261], ESCMID [93], Bodmann *et al.* [43]).

Precautions regarding sodium load

One gram of fosfomycin, corresponding to 1.32 g of disodium fosfomycin, delivers 14.5 mmol sodium into the body, thereby increasing the risk of hypernatraemia or hypokalaemia. According to the Summary of Product Characteristics, administration of fosfomycin at high doses and/or during prolonged treatment should therefore be accompanied by adequate serum electrolyte monitoring to allow excessive sodium loading to be avoided, particularly in patients with congestive heart failure and digitalis-treated heart failure patients (possible hypokalaemia). These patients may have a tendency to develop oedema and secondary hyperaldosteronism. An increase in the infusion length and/or a reduction to the individual dose (with more frequent administration) could also be considered. High sodium loading may also result in secondary elevation of potassium excretion, requiring potassium replacement (Stille *et al.* [317], Traunmüller *et al.* [329], Falagas *et al.* [98]). However, hypokalaemia is a common observation in ICU patients and usually asymptomatic, and medication is merely one possible explanation (Gennari [119]).

A reduced ability to excrete large amounts of sodium has been described in full-term neonates as compared to older infants (Atiyeh *et al.* [20]). In contrast, low tubular reabsorption of sodium and diminished distal tubule responsiveness to aldosterone have been reported in immature neonates, leading to an increased risk of negative sodium balance (Atiyeh *et al.* [20], Al-Dahhan *et al.* [7]). With a partial dose of 50–100 mg/kg of fosfomycin in new-borns and infants up to 12 kg body weight, 1.5–17.4 mmol sodium enter the bloodstream – an amount which should not cause problems (Atiyeh *et al.* [20], Al-Dahhan *et al.* [7]).

Effects on the oropharyngeal and intestinal flora

Unlike other antibiotics with wide-spectrum activity against anaerobic microorganisms, fosfomycin does not usually produce any significant alteration to the intestinal or oropharyngeal flora. Hendlin *et al.* reported that treatment with fosfomycin calcium (500 mg every 6 h) for one month did not change the gut flora in terms of anaerobes, yeasts, or staphylococci, but reduced the *E. coli* count and increased *Enterobacter* and *Klebsiella* counts. This led to a change in stool consistency. The intestinal flora returned to the pre-treatment state within two weeks of treatment cessation (Hendlin *et al.* [145]). Another study investigated the effects of 14 different antibiotics in 144 patients undergoing bowel surgery. Fosfomycin did not cause any changes in gut flora or increases in resistance to itself (Andåker *et al.* [15]). Further investigations of the intestinal flora of 8 healthy volunteers administered 5 g fosfomycin every 12 h demonstrated decreases in the numbers of *E. coli* and *Enterococcus*, but no changes in Bacteroides, anaerobic lactobacilli, or the oropharyngeal flora (Knothe *et al.* [180]). One study examined the effects of 10–15 g fosfomycin per day in the therapy of chronic osteitis in 75 patients. Only 3 patients showed mild gastrointestinal side effects in the form of diarrhoea (Roth *et al.* [285]).

Safety in neonates and children

Fosfomycin is well tolerated by neonates and children, even after several months of administration (Katznelson *et al.* [174]). In another study, fosfomycin was administered to 24 children with *S. marcescens* septicaemia for 14–28 days, leading to cure of the infection in 21/24 (87.5%) of the children without any significant adverse events reported (Baquero *et al.* [26]).

In a clinical trial, 103 children aged 0.1–15.5 yr (mean 6.5, median 6.9) suffering from acute haematogenous osteomyelitis were treated with intravenous fosfomycin alone (n = 23) or with fosfomycin combination therapy (n = 47), or other regimens without fosfomycin (n = 33). The lowest rate of side effects, with just one case of mild diarrhoea, was in the fosfomycin-only group (Corti *et al.* [68]).

In another study, 57 paediatric cancer patients (median age 7.1 yr) were treated with 150 mg/kg/d fosfomycin for a variety of indications. No adverse effects and no cases of hypernatraemia were detected, despite an additional 2 mmol/kg/d sodium intake. None of the patients died as a result of infection (Hepping *et al.* [147]).

No nephrotoxic effects, no hypersensitivity, and no adverse reactions to fosfomycin therapy (200 mg/kg/d) were seen among 10 children aged 11 months to 12 years receiving treatment for bacterial pulmonary processes (Llorens *et al.* [204]).

With respect to paediatric patients, no differences were found in comparison with the overall population in relation to reported adverse events rates, indicating equally high tolerability in children, as reported in a recent review of the clinical literature (Grabein *et al.* [126]).

In the most recent and well-designed study to evaluate the safety and pharmacological profile of fosfomycin in neonates, no impact of fosfomycin on serum sodium or diarrhoea was reported in a population of 61/120 neonates that received i. v. fosfomycin in a dosage of 100 mg/kg BW twice daily. No significant increase in potassium levels was observed in the standard of care plus fosfomycin treated infants in comparison to standard of care alone (Obiero *et al.* [246]).

Overall, a beneficial safety profile has been reported for fosfomycin in neonates and children.

Safety in pregnancy and lactation

The use of fosfomycin during pregnancy is not strictly contraindicated (pregnancy category B) (Roussos *et al.* [286]). The use of oral fosfomycin was described as a safe therapy in pregnancy based on a large number of pregnancies analysed (Mannucci *et al.* [208]). In a large observational cohort study analysing prospectively ascertained pregnancies including 152 women exposed to fosfomycin in the first trimester of pregnancy did not indicate an increased risk of adverse pregnancy outcome after fosfomycin exposure during early pregnancy (Philipps *et al.* [265]). However, for precautionary reasons, it is recommended that fosfomycin should only be used during pregnancy if no other option is apparent and the benefit clearly outweighs the risk (see Summary of Product Characteristics).

Small quantities of fosfomycin enter breast milk (Martindale [213]). Fosfomycin should therefore not be administered during lactation, unless clearly indicated.

4.3 Overall safety profile

Fosfomycin is not metabolised by the liver and has no known clinically relevant pharmacological interactions with other drugs, stimulants, or foodstuffs. Fosfomycin is generally well tolerated in a variety of patient populations. The use of fosfomycin is not restricted by age, and it is licensed for use in premature neonates. The most commonly reported adverse reactions during treatment are dysgeusia, hypernatraemia, hypokalaemia, erythematous eruption, and injection site phlebitis, occurring in up to 10% of patients. No additional or different side effects have been seen in patients receiving high fosfomycin doses. The associated increases in sodium intake during high-dose fosfomycin therapy should be monitored in terms of serum electrolyte levels. Intravenous fosfomycin should only be recommended in nursing or lactating patients if clearly indicated, even though no evidence of teratogenicity is present in the literature. Fosfomycin has been found to have a very good safety and tolerability profile in the neonatal and paediatric patient populations.

In conclusion, fosfomycin has been shown to be a safe and well-tolerated antimicrobial agent in combatting infections in patients of any age. Its safety profile is favourable, especially when compared with other antibiotics, such as aminoglycosides, quinolones, tetracyclins, glycopeptides, or polymyxins.

5 References

5 References

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6 Summary of Product Characteristics (SmPC)

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Name and active ingredients: Fomicyt 40 mg/ml powder for solution for infusion. One ml of reconstituted solution contains 40 mg fosfomycin. 2 g presentation: Each bottle with 2.69 g of powder contains 2.64 g disodium fosfomycin, corresponding to 2 g fosfomycin and 0.64 g sodium, for reconstitution in 50 ml of solvent. Fomicyt 4 g presentation: Each bottle with 5.38 g of powder contains 5.28 g disodium fosfomycin, corresponding to 4 g fosfomycin and 1.28 g sodium, for reconstitution in 100 ml of solvent. Fomicyt 8 g presentation: Each bottle with 10.76 g of powder contains 10.56 g disodium fosfomycin, corresponding to 8 g fosfomycin and 2.56 g sodium, for reconstitution in 200 ml of solvent **Indications:** Treatment of the following infections in all age groups when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment: complicated urinary tract infections, infective endocarditis, bone and joint infections, hospital-acquired pneumonia, including ventilator-associated pneumonia, complicated skin and soft tissue infections, bacterial meningitis, complicated intra-abdominal infections, bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Consideration should be given to official guidance on the appropriate use of antibacterial agents. **Dosage and administration:** Adults and adolescents 12 years, > 40 kg and with normal renal function (creatinine clearance > 80 ml/min): complicated urinary tract infection 12–24 g in 2–3 divided doses, bone and joint infections 12–24 g in 2–3 divided doses, infective endocarditis 12-24 g in 2–3 divided doses, hospital-acquired pneumonia including ventilator-associated pneumonia 12–24 g in 2–3 divided doses; complicated skin and soft tissue infections 12–24 g in 2–3 divided doses; bacterial meningitis 16–24 g in 3–4 divided doses; complicated intra-abdominal infections 12–24 g in 2–3 divided doses; bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above 12–24 g in 2–3 divided doses. Individual doses must not exceed 8 g. Dose reductions in patients with renal impairment are required (please refer to the SmPC for further information). Paediatric population: for neonates, infants and children <12 years of age (<40 kg) the dosage should be based on age and body weight (please refer to the SmPC for further information). Method of administration: intravenous infusion only. The solvent must be water for injections, 5% or 10% glucose infusion. The duration of infusion should be at least 15 minutes for the 2 g pack size, at least 30 minutes for the 4 g pack size and at least 60 minutes for the 8 g pack size. Please refer to the SmPC for further information. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions:** It is recommended that fosfomycin is administered as part of a combination antibacterial drug regimen to reduce the risk of selecting for resistance. It is recommended that fosfomycin is selected to treat the listed indications only when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment. Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment. If such reactions occur, treatment with fosfomycin must be discontinued immediately and adequate emergency measures must be initiated.. Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported. It is important to consider this diagnosis in patients presenting with diarrhoea during or subsequent to administration of Fomicyt. Sodium and potassium levels should be monitored regularly in patients receiving fosfomycin, in particular during prolonged treatment. Given the high content of sodium (0.32 grams) per gram of fosfomycin, the risk of hypernatraemia and fluid overload should be assessed before starting treatment, especially in patients with a history of congestive heart failure or underlying comorbidities such as nephrotic syndrome, liver cirrhosis, hypertension, pulmonary oedema or hypoalbuminemia as well as in neonates under sodium restriction. A low-sodium diet is recommended during treatment. An increase in the infusion length and/or a reduction to the individual dose (with more frequent administration) could also be considered. Fosfomycin may decrease potassium levels in serum or plasma, therefore potassium supplementation should be always considered. In patients receiving fosfomycin intravenously haematological reactions including neutropenia or agranulocytosis have occurred. Please refer to the SmPC for further information. **Interactions:** Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotic therapy. The severity of the infection or inflammation, patient age and general state of health appear to be risk factors. Under these circumstances, it is difficult to determine to what extent the infection itself or its treatment play a role in the INR imbalance. However, certain classes of antibiotics are more involved, particularly: fluoroquinolones, macrolides, cyclins, cotrimoxazole, and certain cephalosporins. **Undesirable effects (see SmPC for full details):** Common: dygeusia, hypernatraemia, hypokalemia, erythematous eruption, injection site phlebitis. Uncommon: headache, nausea, vomiting, diarrhea, blood alkaline phosphatase increased (transient), transaminases increased (ALAT, ASAT), gamma-GT increased, rash, asthenia. Very rare: anaphylactic reactions including anaphylatic shock and hypersensitivity, Unknown frequency: agranulocytosis (transient), leucopenia, thrombocytopenia, neutropenia, antibiotic-associated colitis, hepatitis, pruritus, urticaria, angioedema. Please refer to the SmPC for further information. **Pack size:** 30/50/100 ml clear glass bottle with rubber stopper and pull off cap containing 2 g, 4 g, or 8 g. **Date of preparation:** October 2020

InfectoFos 2g/3g/5g/8 g. Pulver z. Herst. einer Infusionslsg. **Wirkst.:** Fosfomycin. **Zus.:** 1 Flasche enth. 2,0/3,0/5,0/8,0 g Fosfomycin. **Sonst. Bestandt.:** Bernsteinsäure. **Anw.:** *In allen Altersgr. z. Behandl. d. folgenden Infekt., wenn Einsatz der f. die Erstbehandl. allgemein empfohlenen antibakt. Mittel als ungeeignet erachtet wird: komplizierte Harnwegsinfekt., infektiöse Endokarditis, Knochen- u. Gelenkinfekt., im Krankenhaus erworbene Pneumonie, einschließl. Beatmungspneumonie, komplizierte Haut- u. Weichgewebeinfekt., bakterielle Meningitis, komplizierte intraabdominelle Infekt., Bakteriämie.* **Gegenanz:** Überempf. gg. den Wirkstoff od. einen der sonstigen Bestandteile. **Warnhinw.:** Enth. 320 mg Natrium pro 1 g Fosfomycin, entspr. 16 % der v. der WHO f. Erw. empfohl. max. tägl. Natriumaufn. m. der Nahrung v. 2 g. In der Folge ist auch Hypernatriämie oder Hypokaliämie mögl. Natrium- u. Kaliumspiegel regelm. kontrollieren. Ggf. Kalium substituieren. Während d. Behandl. wird eine natriumarme Ernährung empfohlen. Für weitere Warnhinweise s. Fachinformation. **Nebenw.:** Agranulozytose (vorübergehend), Leukopenie, Thrombozytopenie, Neutropenie; anaphylakt. Reakt. einschließl. anaphylakt. Schock u. Überempf.; Dysgeusie, Kopfschm.; Hypernatriäme, Hypokaliämie; Übelk., Erbrechen, Diarrhö, Antibiotika-assoziierte Kolitis; alkalische Phosphate im Blut erhöht, Transaminasen erhöht (ALAT, ASAT), Gamma-GT erhöht, Hepatitis; erythematöser Ausschlag, Ausschlag, Angioödem, Pruritus, Urtikaria; Venenentzünd. an d. Injektionsstelle, Asthenie. **Verschreibungspflichtig.** Stand: 08/2020. **InfectoPharm Arzneimittel und Consilium GmbH, Von-Humboldt-Str. 1, 64646 Heppenheim**

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