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Guidelines

Intravenous administration of antibiotics by prolonged and continuous infusion

1. Introduction

The use of prolonged and continuous infusions to maximize the pharmacokinetic and pharmacodynamic parameters of antibiotics, which effectiveness is time-dependent, has increased significantly over the past years. Many national and international guidelines recommend using such administration methods [1,2], based on a large body of scientific literature. Prolonged and continuous infusions of antibiotics pose several risks, ranging from therapeutic ineffectiveness to degradation product toxicity, linked with antibiotic stability in infusions. The various interdependent parameters that modify the stability of antibiotics should be known and considered in order to suggest appropriate treatment regimens.

Several literature reviews with good practice proposals were published in 2016 [3], followed by another literature review in 2021 focusing on outpatient antibiotic therapy [4,5]. As numerous limitations were raised, the authors of the present work decided to compile guidelines that would take into consideration the various French medical specialties expertise.

2. Methods

Under the coordination of the SPILF, the drafting group of the present guidelines brought together the various French scientific societies: Société Française de Pharmacie Clinique (SFPC), Infostab (authors of the website STABILIS), Groupe des Référents en Infectiologie d'Ile-de-France (GRIF), Société de Réanimation de Langue Française (SRLF), Société Française d'Anesthésie et Réanimation (SFAR), réseau des OMEDITs (RESOMEDIT), and Société Française de Pharmacologie et de Thérapeutique (SFPT).

The first step consisted in determining the various interdependent parameters that modify the stability of antibiotics. Temperature, light exposure, diluting solute, concentration, and container materials were all taken into account. Literature review criteria allowing for selecting antibiotic stability parameters in each administration setting are detailed below. Stabilities selected following the literature review are presented in Table 1 (stability at room temperature) and Table 2 (stability above 30 °C in an elastomeric infusion pump).

The present guidelines neither address indications for prolonged or continuous intravenous infusions nor the choice of medical device used for administration. However, a practical guide in **Appendix 1** (supplemented by **Table S1** and practical guides in **Appendix 2**) provide information to guide prescribers in choosing medical devices (gravity infusion devices, elastomeric infusion pumps, volumetric infusion pumps, electric syringe pumps).

Finally, common dosage ranges were determined for each molecule, in line with the dosages recommended by the French microbiological society (French acronym CA-SFM) [6]. Recommended administration schedules are grouped into two tables: one for hospital administration schedules (**Table S2**) and another one for home administration schedules (**Table S3**). A selection of the main antibiotics at the most frequent dosages is detailed below in Table 3 (hospital setting) and in Table 4 (focusing on elastomeric infusion pumps).

All data presented here are subject to regular updating based on the publication of new drug stability studies, with the aim of simplifying the administration of antibiotics in outpatient settings.

To improve ergonomics, such pieces of data will be entered into a search engine to enable rapid access to the desired administration schedules on any computer workstation connected to the Internet.

3. General principles and recommendations for selecting antibiotic stability studies

R-1: *Which parameters influence antibiotic stability?*

4. Parameters that should be taken into account are concentration, solvent, container, temperature, and exposure to light

Parameters influencing antibiotic stability are molecule concentration, diluting solvent, finalized preparation container, and storage conditions (exposure to light or non-exposure to light, temperature).

R2: *Which physico-chemical techniques should be used to study antibiotic stability?*

Mandatory: at least one separation technique (high-performance liquid chromatography or HPLC; capillary electrophoresis) and a visual check of the finalized preparation will be required to include a study in the present guidelines.

Additional: if pH variation has been studied, a maximum variation of 1 unit will be accepted to select the publication.

5. Chemical stability

A separation technique must be used when studying the chemical

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Table 1
Stability of antibiotics at room temperature in polyethylene, polyolefin or polypropylene containers.

Molecule	Solvent	Concentration	Stability	Comment	Reference
amoxicillin	NaCl 0.9 %	5 mg/mL	24 h		[7]
	NaCl 0.9 %	20 mg/mL	12 h		[8]
	G 5 %	10 mg/mL	2 h	Instability in glucose 5 %: not recommended for prolonged infusions but can be used intermittently	[9]
		50 mg/mL	1 h		[9]
amoxicillin + clavulanic acid	NaCl 0.9 %	20 mg/mL	4 h	Expressed in mg of amoxicillin	[10]
ampicillin + sulbactam	NaCl 0.9 %	20 mg/mL	24 h	Expressed in mg of ampicillin	[11]
aztreonam	NaCl 0.9 % or G 5 %	10–125 mg/mL	>24 h		[8,12,13]
benzylpenicillin	NaCl 0.9 %	0.13 mIU/mL	12 h		[14]
cefazolin	G 5 %	125 mg/mL	24 h		[8]
	NaCl 0.9 %	10–125 mg/mL	>24 h		[7,8,15]
cefepime	NaCl 0.9 % or G 5 %	2.5–125 mg/mL	24 h		[8,16–19]
cefiderocol	NaCl 0.9 % or G 5 %	62.5 mg/mL	24 h		[8]
cefotaxime	G 5 %	10–20 mg/mL	24 h		[7,20,21]
	NaCl 0.9 %	10–50 mg/mL	24 h		[7,20,20,21]
	NaCl 0.9 % or G 5 %	83.3–125 mg/mL	6 h		[8,22]
cefoxitin	G 5 %	125 mg/mL	12 h		[8]
ceftaroline	NaCl 0.9 %	4–12 mg/mL	6 h		[23]
ceftazidime	NaCl 0.9 %	20–125 mg/mL	24 h		[7,8]
	G 5 %	125 mg/mL	8 h		[8]
ceftazidime + avibactam	NaCl 0.9 % or G 5 %	125 mg/mL	24 h	Expressed in mg of ceftazidime	[8]
ceftobiprole	NaCl 0.9 %	2.67 mg/mL	8 h	24 h away from direct sun light	[24]
	G 5 %	2.67 mg/mL	8 h	12 h away from direct sun light	[24]
ceftolozane + tazobactam	NaCl 0.9 % or G 5 %	62.5 mg/mL	48 h	Expressed in mg ceftolozane	[8]
ceftriaxone	NaCl 0.9 % or G 5 %	40 mg/mL	24 h		[25]
	NaCl 0.9 %	20 mg/mL	24 h		[7]
cefuroxime	NaCl 0.9 %	5–90 mg/mL	24 h		[26–28]
	G 5 %	5 mg/mL	24 h		[27]
clindamycin	NaCl 0.9 % or G 5 %	6 and 12 mg/mL	>24 h		[29]
	NaCl 0.9 %	60 and 150 mg/mL	>24 h		[12,30]
cloxacillin	NaCl 0.9 % or G 5 %	5–125 mg/mL	24 h		[8,31]
colistin	NaCl 0.9 %	1.6 mg/mL or 0.02 mIU/mL	24 h		[32]
ertapenem	NaCl 0.9 %	10–20 mg/mL	6 h		[33,34]
		100 mg/mL	5 h		[35]
fosfomycin	G 5 %	40 mg/mL	24 h		[36]
imipenem + cilastatin	NaCl 0.9 % or G 5 %	5 mg/mL	4 h	Expressed in mg of imipenem	[37,38]
imipenem + cilastatin + relebactam	NaCl 0.9 % or G 5 %	5 mg/mL	2 h	Expressed in mg of imipenem	[39]
meropenem	NaCl 0.9 %	10 mg/mL at 41.7 mg/mL	8 h		[8,40]
	G 5 %	41.7 mg/mL	4 h		[8]
meropenem + vaborbactam	NaCl 0.9 %	4–8 mg/mL	12 h	Expressed in mg of meropenem	[41]
oxacillin	NaCl 0.9 %	10 and 100 mg/mL	>24 h		[42]
piperacillin	NaCl 0.9 % or G 5 %	10–125 mg/mL	24 h		[8]
piperacillin + tazobactam	NaCl 0.9 % or G 5 %	20–200 mg/mL	24 h	Expressed in mg of piperacillin	[8,43,44]
sulfamethoxazole + trimethoprim	G 5 %	3.3–4.2 mg/mL	4 h	Expressed in mg of sulfamethoxazole	[45]
teicoplanin	No data				
temocillin	NaCl 0.9 % or G 5 %	125 mg/mL	24 h		[46]
vancomycin	NaCl 0.9 % or G 5 %	5 mg/mL	24 h	Peripheral venous catheter	[47]
	NaCl 0.9 % or G 5 %	41.7–83.3 mg/mL	24 h	Central venous catheter	[8,48–50]

stability of drugs; most frequently, high-performance liquid chromatography (HPLC) and capillary electrophoresis. Other techniques may be used more rarely, such as gas chromatography, thin-layer chromatography (classic or high performance). These techniques enable degradation products to be identified, unlike non-separation techniques such as ultraviolet–visible spectrometry.

pH measurement is an additional technique used to study chemical stability, not required in the present guidelines if a separation technique has been used. If pH measurement has been performed, the variation in pH at various measuring times should not exceed 1 unit, even if the variation in active molecule concentration is adequate.

6. Physical stability

A visual check must always be carried out when studying physical stability to look for precipitates, crystallization, or significant variation

Table 2
Stability of antibiotics at a minimum of 30 °C in elastomeric silicone or polyisoprene containers.

Molecule	Material	Solvent	Concentration	Stability	Comment	Reference
amoxicillin	S	NaCl 0.9 %	12.5 mg/mL	12 h		[51]
			25 mg/mL	8 h		
amoxicillin + clavulanic acid	No data					
ampicillin + sulbactam	No data					
aztreonam	P	NaCl 0.9 % or G 5 %	50 mg/mL	24 h		[8]
benzylpenicillin	No data					
cefazolin	P	NaCl 0.9 % or G 5 %	50 mg/mL	–	Unstable at 37 °C	[8]
	P	NaCl 0.9 % or G 5 %	12.5–25 mg/mL	12 h		[52]
cefepime	S	NaCl 0.9 % or G 5 %	12.5 mg/mL	12 h		ID*
cefiderocol	P	NaCl 0.9 % or G 5 %	25 mg/mL	6 h		[8]
cefoxitin	S	NaCl 0.9 % or G 5 %	12.5 mg/mL	12 h		[53]
		NaCl 0.9 % or G 5 %	25 mg/mL	–	Unstable at 37 °C	[8]
cefotaxime	S	NaCl 0.9 % or G 5 %	12.5 mg/mL	12 h		ID*
ceftaroline	P	NaCl 0.9 %	6 mg/mL	12 h		[54]
		G 5 %	6 mg/mL	6 h		
ceftazidime	S	NaCl 0.9 %	12.5–25 mg/mL	12 h		ID*
		G 5 %	12.5 mg/mL	12 h		
	P	NaCl 0.9 % or G 5 %	25 mg/mL	8 h		[8]
ceftazidime + avibactam	P	NaCl 0.9 %	25 mg/mL	12 h	Expressed in mg of ceftazidime	[8]
		G 5 %	25 mg/mL	–	Unstable at 37 °C	[8]
ceftobiprole	No data					
ceftolozane + tazobactam	P	NaCl 0.9 %	25 mg/mL	12 h	Expressed in mg ceftolozane	[8]
		G 5 %	25 mg/mL	8 h		
	P or S	NaCl 0.9 %	3.33–13.33 mg/mL	18 h		[55]
ceftriaxone	No data					
cefuroxime	No data					
clindamycin	No data					
cloxacillin	P	NaCl 0.9 % or G 5 %	50–100 mg/mL	–	Unstable at 37 °C	[8]
colistin	No data					
ertapenem	No data					
fosfomycin	No data					
imipenem	No data					
imipenem + relebactam	No data					
meropenem	No data					
meropenem + vaborbactam	No data					
oxacillin	P	NaCl 0.9 %	50 mg/mL	8 h		[56,57]
piperacillin	S	NaCl 0.9 %	50–133.3 mg/mL	24 h		ID*
		G 5 %	50 mg/mL	24 h		ID*
piperacillin + tazobactam	P	NaCl 0.9 % or G 5 %	66.7 mg/mL	24 h	Expressed in mg of piperacillin	[8]
sulfamethoxazole + trimethoprim	No data					
teicoplanin	No data					
temocillin	P	NaCl 0.9 %	25 mg/mL	24 h		[8]
vancomycin	P	NaCl 0.9 % or G 5 %	25–37.5 mg/mL	24 h		[8]

* ID: unpublished internal data.

of color.

Subvisual assessment (particle counting, microscopic analysis, or turbidimetry) may be undertaken to look for particles not visible to the naked eye. If these additional studies have not been performed, the studies may still be eligible for the present guidelines.

R-3: *Which toxic degradation products should be taken into account for antibiotic stability?*

Only degradation products which toxicity has been proven in the literature will be taken into account in the present guidelines.

Only degradation products which toxicity has been proven in the literature will be taken into account. Accepted thresholds must be supported by literature data. Toxicity levels indicated in the European Pharmacopoeia, or in any other Pharmacopoeia, determined for raw materials cannot necessarily be applied to injectable preparations.

R-4: *What is the acceptable variation in the active molecule concentration?*

Concentration higher than or equal to 90 % of the initial concentration will be accepted as the stability threshold.

Drug stability studies are usually performed at thresholds of 95 % or 90 % residual active molecule. The main purpose of these thresholds is to validate the quantity of product administered when a drug is prepared in advance, or when a product is stored in its primary packaging (use-by date). When an antibiotic is prepared extemporaneously for prolonged or continuous administration, the concentration of the active molecule administered decreases over time until a minimum acceptable threshold is reached. Considering this gradual reduction in the concentration and the therapeutic margin of antibiotics, these guidelines are based on a stability threshold of 90 % residual active molecule.

R-5: *Can published concentration data be extrapolated to other antibiotic concentrations?*

Extrapolation of published concentration data will be accepted in the following cases

- Concentrations between two validated concentrations for the same solvent.
- Concentrations below a validated concentration, on a case-by-case basis.

Being able to extrapolate data – within the limits of scientific acceptability – is necessary because all concentrations useful in clinical practice have not been studied. In the case of antibiotics, it is mainly high concentrations that affect stability, through lack of solubility and precipitation.

Considering the sometimes-limited literature data on concentration

Table 3
Methods of administration by prolonged or continuous infusion in hospital settings, for the main antibiotics.

Molecule	Solvent	Maximum concentration	Infusion method	Prescribed daily dose	Device	Dilution and administration
amoxicillin	NaCl 0.9 %	20 mg/mL	Continuous	8	Volumetric pump	4 g in 200 to 250 mL over 12 h x2/day
			Continuous	10	Volumetric pump	5 g in 250 mL over 12 h x2/day
			Continuous	12	Volumetric pump	6 g in 300 to 500 mL over 12 h x2/day
			Continuous	16	Volumetric pump	8 g in 400 to 500 mL over 12 h x2/day
aztreonam	NaCl 0.9 %/G 5 %	125 mg/mL	Continuous	6	Electric syringe pump	6 g in 48 mL over 24 h x1/day
			Prolonged	6	Electric syringe pump	2 g in 48 mL over 3–4 h x3/day
			Prolonged	8	Electric syringe pump	2 g in 48 mL over 3–4 h x4/day
cefazolin	NaCl 0.9 %G 5 %	125 mg/mL	Continuous	6	Electric syringe pump	6 g in 48 mL over 24 h x1/day
			Continuous	8	Electric syringe pump	4 g in 48 mL over 12 h x2/day
			Continuous		Volumetric pump	8 g in 100 mL over 24 h x1/day
cefepime	NaCl 0.9 %/G 5 %	125 mg/mL	Continuous	4	Electric syringe pump	4 g in 48 mL over 24 h x1/day
			Continuous	6	Electric syringe pump	6 g in 48 mL over 24 h x1/day
			Prolonged	6	Electric syringe pump	2 g in 48 mL over 3–4 h x3/day
cefiderocol	NaCl 0.9 %/G 5 %	62.5 mg/mL	Continuous	6	Electric syringe pump	3 g in 48 mL over 12 h x2/day
			Continuous	6	Volumetric pump	6 g in 100 mL over 24 h x1/day
			Prolonged	6	Electric syringe pump	2 g in 48 mL over 3–4 h x3/day
cefotaxime	NaCl 0.9 %	50 mg/mL	Continuous	12	Volumetric pump	12 g in 250 mL over 24 h x1/day
			Continuous	16	Volumetric pump	16 g in 500 mL over 24 h x1/day
			Continuous	12	Electric syringe pump	3 g in 48 mL over 6 h x4/day
			Continuous	16	Electric syringe pump	4 g in 48 mL over 6 h x4/day
cefoxitin	G 5 %	125 mg/mL	Continuous	8	Electric syringe pump	4 g in 36 mL over 12 h x2/day
ceftazidime	NaCl 0.9 %	125 mg/mL	Continuous	4	Electric syringe pump	2 g in 48 mL over 12 h x2/day
			Continuous	6	Electric syringe pump	3 g in 48 mL over 12 h x2/day
			Continuous	8	Electric syringe pump	4 g in 48 mL over 12 h x2/day
			Prolonged	6	Electric syringe pump	2 g in 48 mL over 3–4 h x3/day
ceftazidime + avibactam	NaCl 0.9 %/G 5 %	125 mg/mL	Continuous	6	Electric syringe pump	2 g in 48 mL over 8 h x3/day
ceftolozane + tazobactam	NaCl 0.9 %/G 5 %	62.5 mg/mL	Continuous	6	Electric syringe pump	3 g in 48 mL over 12 h x2/day
cloxacillin	NaCl 0.9 %/G 5 %	125 mg/mL	Continuous	8	Electric syringe pump	4 g in 48 mL over 12 h x2/day
			Continuous	10	Electric syringe pump	5 g in 48 mL over 12 h x2/day
			Continuous	12	Electric syringe pump	6 g in 48 mL over 12 h x2/day
			Continuous	16	Volumetric pump	16 g in 250 mL over 24 h x1/day
fosfomycin	G 5 %	40 mg/mL	Prolonged	12	Volumetric pump	4 g in 500 mL over 3–4 h x3/day
			Prolonged	16	Volumetric pump	4 g in 500 mL over 3–4 h x4/day
meropenem	NaCl 0.9 %	41.7 mg/mL	Continuous	6	Electric syringe pump	2 g in 48 mL over 8 h x3/day
			Prolonged	6	Electric syringe pump	2 g in 48 mL over 8 h x3/day
meropenem + vaborbactam	NaCl 0.9 %	8 mg/mL	Continuous	6	Volumetric pump	2 g in 250 mL over 8 h x3/day
			Prolonged	6	Volumetric pump	2 g in 250 mL over 3–4 h x3/day
oxacillin	NaCl 0.9 %	100 mg/mL	Continuous	8	Electric syringe pump	4 g in 48 mL over 12 h x2/day
			Continuous	10	Electric syringe pump	5 g in 48 mL over 12 h x2/day
			Continuous	12	Volumetric pump	12 g in 250 mL over 24 h x1/day
			Continuous	16	Volumetric pump	16 g in 250 mL over 24 h x1/day
piperacillin	NaCl 0.9 %/G 5 %	125 mg/mL	Continuous	12	Electric syringe pump	6 g in 48 mL over 12 h x2/day
			Continuous	12	Volumetric pump	12 g in 100 mL over 24 h x1/day

(*continued on next page*)

Table 3 (*continued*)

Molecule	Solvent	Maximum concentration	Infusion method	Prescribed daily dose	Device	Dilution and administration
			Continuous	16	Volumetric pump	16 g in 250 mL over 24 h x1/day
			Prolonged	12	Electric syringe pump	4 g in 48 mL over 3–4 h x3/day
			Prolonged	16	Electric syringe pump	4 g in 48 mL over 3–4 h x4/day
piperacillin + tazobactam	NaCl 0.9 %/G 5 %	200 mg/mL	Continuous	12	Electric syringe pump	6 g in 48 mL over 12 h x2/day
			Continuous	12	Volumetric pump	12 g in 100 mL over 24 h x1/day
			Continuous	16	Electric syringe pump	8 g in 48 mL over 12 h x2/day
			Prolonged	12	Electric syringe pump	4 g in 48 mL over 3–4 h x3/day
			Prolonged	16	Electric syringe pump	4 g in 48 mL over 3–4 h x4/day
temocillin	NaCl 0.9 %/G 5 %	125 mg/mL	Continuous	6	Electric syringe pump	6 g in 48 mL over 24 h x1/day

Table 4
Methods of administration for continuous infusion using elastomeric infusion pumps, for the main antibiotics.

Molecule	Solvent	Maximum concentration	Prescribed daily dose (g)	Dilution and administration	Pump volume	Pump material*	Number of times a nurse needs to visit
amoxicillin	NaCl 0.9 %	12.5 mg/mL	8	4 g in 480 mL over 12 h x2/day	320–480 mL	S	2
			10	5 g in 480 mL over 12 h x2/day	400–600 mL	S	2
			12	6 g in 480 mL over 12 h x2/day	480–600 mL	S	2
aztreonam	NaCl 0.9 %/ G 5 %	50 mg/mL	6	6 g in 120 mL over 24 h x1/day	120–150 mL	P	1
			8	8 g in 150 mL over 24 h x1/day	146–150 mL	P	1
cefazolin	NaCl 0.9 %/ G 5 %	25 mg/mL	6	3 g in 240 mL over 12 h x2/day	240–480 mL	P	2
			8	4 g in 240 mL over 12 h x2/day	320–600 mL	P	2
cefepime	NaCl 0.9 %/ G 5 %	12.5 mg/mL	4	2 g in 240 mL over 12 h x2/day	160–240 mL	S	2
			6	3 g in 240 mL over 12 h x2/day	240–250 mL	S	2
cefotaxime	NaCl 0.9 %/ G 5 %	12.5 mg/mL	8	4 g in 480 mL over 12 h x2/day	320–480 mL	S	2
			10	5 g in 480 mL over 12 h x2/day	400–480 mL	S	2
			12	6 g in 480 mL over 12 h x2/day	480–500 mL	S	2
cefoxitin	NaCl 0.9 %/ G 5 %	12.5 mg/mL	8	4 g in 480 mL over 12 h x2/day	320–480 mL	S	2
ceftazidime	NaCl 0.9 %	25 mg/mL	4	2 g in 120 mL over 12 h x2/day	80–160 mL	S	2
			6	3 g in 240 mL over 12 h x2/day	120–240 mL	S	2
ceftazidime + avibactam	NaCl 0.9 %	25 mg/mL	6	3 g in 120 mL over 12 h x2/day	120–240 mL	P	2
ceftolozane + tazobactam	NaCl 0.9 %	25 mg/mL	6	3 g in 120 mL over 12 h x2/day	120–600 mL	P	2
cloxacillin	NaCl 0.9 %/ G 5 %	50 mg/mL	Unstable in pump at 37 °C			–	–
oxacillin	NaCl 0.9 %	50 mg/mL	12	4 g in 96 mL over 8 h x3/day	80–100 mL	P	3
piperacillin	NaCl 0.9 %	133 mg/mL	12	12 g in 120 mL over 24 h x1/day	90–240 mL	S	1
			16	16 g in 240 mL over 24 h x1/day	120–320 mL	S	1
piperacillin + tazobactam	NaCl 0.9 %/ G 5 %	67 mg/mL	12	12 g in 240 mL over 24 h x1/day	180–240 mL	P	1
			16	16 g in 240 mL over 24 h x1/day	240–250 mL	P	1
temocillin	NaCl 0.9 %	25 mg/mL	6	6 g in 240 mL over 24 h x1/day	240–250 mL	P	1

* S: silicone / P: polyisoprene.

ranges tested, which are not always compatible with clinical practice, and taking into account the stability data for antibiotics in solution, which tend to increase stability at lower concentrations, an extrapolation of the x1.5 dilution may be considered acceptable in some cases:

- Standardization of electric syringe pump use by increasing volumes to 48 mL.
- No compatible elastomeric infusion pump on the market if the dilution is not extrapolated.

R-6: *Can published data be extrapolated between different dilution solvents for antibiotics?*

Extrapolation between solvents of different natures (glucose solution, saline solution, polyionic solution, water-for-injection solution) will not be accepted. Extrapolation between solvents of the same nature but at different concentrations (glucose 2.5 % and glucose 5 %, NaCl 0.45 % and NaCl 0.9 %) will be accepted.

Solvents can differ significantly in their composition: presence or absence of chloride ions, pH value, electrolyte composition. These differences can have a major impact on molecule stability, and it is not possible to extrapolate stability from one solvent to another.

Examples of differences in characteristics:

- The pH value of the 5 % glucose solution is 4, compared with 6.5 for NaCl 0.9 %.
- Polyionic solutions contain cations responsible for precipitation, such as calcium with ceftriaxone.
- The presence of glucose or ions may cause precipitation or a chemical reaction which may lead to instability compared with a solution prepared with sterile water for injection alone.

R-7: *When should temperatures above 25 °C be taken into account?*

At the minimum, antibiotic stability must be studied under conditions corresponding to room temperature (18–25 °C).

When using elastomeric infusion pumps, stability must be studied at temperatures above 30 °C. In the absence of data at this temperature, the study will be made on a case-by-case basis.

Stability studies must take into account different ranges of temperature, depending on the conditions of preservation/storage/environment of use.

Studies on temperature ranges < 20 °C or between 4 and 8 °C address preservation or storage methods and are therefore not the focus of the present guidelines. Temperature ranges from 18 to 25 °C correspond to room temperature and are in line with practices in hospital wards (with the exception of elastomeric infusion pumps). Lastly, studies > 30 °C correspond to heatwave conditions or to devices placed onto the patient's body (elastomeric infusion pumps).

Data resulting from experimentation on a given, and therefore controlled, temperature range (proven instability) must be distinguished from data not available on other temperature ranges (non-proven instability: case-by-case assessment).

R-8: *Can published data be extrapolated between different antibiotic containers?*

Accepted extrapolations, provided the other parameters are similar

- Containers without PVC and without elastomer (polyethylene [PE], polypropylene [PP], polyolefin [PO]): can be extrapolated between them.
- Containers with PVC: can be extrapolated to containers without PVC or elastomer (PE, PP, PO).
- Unknown containers: can be extrapolated to containers without PVC or elastomer (PE, PP, PO).

Refused extrapolations, to assess on a case-by-case basis

- **Containers with PVC:** stability must have been tested in a similar container.
- **Containers with elastomer:** stability must have been tested in a similar container.
- stability in elastomeric silicone or polyisoprene containers is not interchangeable

Container-content interactions must be taken into account for antibiotic stability. Sorption phenomena (adsorption and absorption) and salting-out phenomena can occur. These phenomena are more prevalent with PVC or elastomer (polyisoprene and/or silicone) containers. IV bags are now mainly made from PVC-free plastics (polyolefin or polyethylene), and syringes from polypropylene. Elastomeric infusion pumps are made of polyisoprene or silicone.

At the high antibiotic concentrations used for prolonged or continuous administration, product loss through sorption is minimal.

R-9: *Can published data on antibiotics be extrapolated in the absence of light exposure?*

Stability extrapolation in the event of exposure to light will be accepted, even if stability has only been tested in an opaque container, with the exception of products for which degradation when exposed to light has been proven in the literature.

When exposed to light, drug photodegradation can occur by catalyzing hydrolysis or oxidation reactions. Photodegradation depends on light intensity, wavelength and duration of exposure. The consequences may be loss of active product or formation of toxic products. While many molecules should be kept away from light, very few require photoprotection during administration, even in case of prolonged or continuous administration (exposure time below 24 h).

Author contributions

All of the authors contributed to the literature review required to compile the present guidelines and to write the manuscript. CO and SD wrote the final version of the manuscript. All of the authors reviewed and approved all of the documents.

Ethical statement

The present guidelines did not require any specific advice from an ethical board.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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