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## **Title**

Subcutaneous antibiotic therapy: the why, how, which drugs and when

## **Intended Category**

Narrative Review

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**Brief summary:**

This study reports the rationale for subcutaneous (SC) administration of antibiotics and its limitations. Evidence suggests that the SC route could be an alternative to the IV route for time-dependent antibiotics in specific situations.

1 **Abstract**

2 **Objectives:** To describe the rationale for subcutaneous (SC) administration of  
3 antibiotics from available published data and to make propositions to help clinicians in  
4 daily practice.

5 **Design:** Narrative review

6 **Setting and participants:** Hospitalized patients, persons in long-term care facilities and  
7 ambulatory care.

8 **Methods:** We searched the MEDLINE/PubMed electronic database for evidence  
9 supporting SC administration of antibiotics, up to September 2019; the results of this  
10 primary search were supplemented by searching the references of the identified articles,  
11 as well as by searching in Google Scholar.

12 **Results:** Regarding tolerability, efficacy, and pharmacokinetic/pharmacodynamic  
13 (PK/PD) profiles, most studies suggest that the SC route could be an alternative to the  
14 IV route, particularly for time-dependent antibiotics and among certain patient  
15 populations, like patients with poor venous access, swallowing disorders or behavioural  
16 disturbance. However, clinical evidence of the benefits and risks of SC antibiotic  
17 administration is still scarce and of low level.

18 **Conclusions and Implications:** SC administration of antibiotics may be useful in  
19 various settings such as in hospitalized patients and among those in long-term care  
20 facilities or being cared for at home. However, further clinical studies are needed to  
21 assess the PK/PD properties, as well as the risks and benefits of SC administration of  
22 antibiotics. In this review, we highlight the potential benefits of SC administration of  
23 antibiotics and address practical recommendations for its use. This information will

- 24 enable improvement of treatment strategies and present the SC route as a potential
- 25 option in specific situations.

## 26 **Subcutaneous antibiotic therapy: Why, how, which drugs, and when**

### 27 **Introduction**

28 Bacterial infections are one of the main causes of morbidity and mortality in the older  
29 population and pose many challenges to the clinician; one of the first challenges is  
30 selecting the route of antibiotic administration. The most frequently used routes for  
31 delivering antibiotics are intravenous (IV), oral, and intramuscular (IM), each one with  
32 benefits and drawbacks.<sup>1</sup>

33 In special populations like older adults, an IV access may become challenging because  
34 of a poor peripheral venous network or agitation. IM access can be associated with pain  
35 and is contraindicated in patients receiving anticoagulants. Moreover, drugs  
36 administered through IM route can inadvertently be delivered to the subcutaneous (SC)  
37 space.<sup>2, 3, 4, 5</sup> Oral administration may be compromised by swallowing disorders, altered  
38 mental state, or by limited treatment options. In addition, the oral bioavailability of  
39 certain antibiotics may be reduced by food-drug, drug-drug interactions, and  
40 gastrointestinal disorders.<sup>2, 3, 4</sup>

41 SC administration may help to circumvent those limitations frequently found in long-  
42 term care facilities, geriatric departments, palliative, and ambulatory care, which could  
43 partially explain why this route is mainly used in those settings.<sup>6</sup> Nevertheless, SC  
44 administration of antibiotics is still off-label for many of them. An up-to-date review on  
45 this issue is needed as a growing body of evidence could further support the use of the  
46 SC route.<sup>7, 8, 9, 10</sup> The main objectives of this review were to analyse the rationale for SC  
47 administration of antibiotics, and make practical propositions to help clinicians in daily  
48 practice, as well as the development of future clinical trials.

### 49 **Methods**

50 We conducted a MEDLINE/PubMed database research up to September 2019, the  
51 results of this primary search were supplemented by reviewing the references of the  
52 identified articles, and by searching Google Scholar. The initial PubMed search terms  
53 were: subcutaneous[All Fields] AND ("anti-bacterial agents"[Pharmacological Action]  
54 OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND  
55 "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All  
56 Fields])) AND "humans"[MeSH Terms]. The initial search provided close to 500  
57 articles. Any abstract that described SC administration of antibiotics in humans was  
58 considered eligible for inclusion. Abstracts that did not described SC administration of  
59 antibiotics, and animal-based studies were excluded. Posters and conference  
60 presentations were included if they described original research. The articles considered  
61 for inclusion were limited to those written in French, English, or Spanish. Finally, 37  
62 articles, and 3 poster presentations were included.

## 63 **Discussion**

### 64 **Why subcutaneous administration?**

#### 65 - **The subcutaneous route**

66 Drugs administered by SC route are delivered into the interstitial space, a fibro-  
67 collagenous network beneath the dermis.<sup>11</sup> Following their delivery, one of the first  
68 things that influences absorption is molecular weight. Small-molecules are absorbed  
69 into the interstitial vasculature by passive diffusion and endothelial permeability.  
70 Whereas high-molecular-weight agents are absorbed in the lymphatic system, which  
71 delays the time to achieve their maximum concentration.<sup>12, 13</sup> Other factors that  
72 influence the rate and extent of drugs absorption are: electric charge, hydrophilicity,  
73 degradation profile, and formulation (*e.g.*, concentration, volume, viscosity, and  
74 excipient profile).<sup>14</sup> In clinical practice, the SC route is routinely used to administer



75 vaccines, insulin, heparin, biological agents, and high-molecular-weight medications  
76 (*e.g.*, immunoglobulins).<sup>15, 16</sup>

77 - **Advantages of subcutaneous administration**

78 The SC route may usefully combine some advantages of both the oral and other  
79 parenteral routes.<sup>17, 18</sup> SC administration of drugs is described as easy to perform (less  
80 demanding for nursing staff), it enables continuous administration of fluids  
81 (hypodermoclysis), or bolus administration of pharmacological agents in diverse  
82 settings.<sup>19, 20, 21, 22</sup> Also, compared to the IV route, the risks of thrombosis and catheter  
83 infections in SC route are less frequent or less severe, however strong evidence from  
84 comparative studies is lacking.<sup>9, 23</sup> Unlike IM route, SC administration is not  
85 contraindicated by anticoagulant therapy, which is common in older adults. In addition,  
86 the SC route has little impact on patient's mobility, which is a central component for the  
87 prevention of functional decline and rehabilitation.<sup>24</sup>

88 Taking into account the mentioned profile, SC administration of antibiotics could find a  
89 place in-hospital care, prolonged outpatient therapy, as well as in long-term care  
90 facilities.<sup>25, 26</sup>

91 - **Limitations of subcutaneous administration**

92 Adverse events (AEs) caused by SC administration of drugs may include pain, oedema,  
93 and inflammation at the injection site (details for AEs are described in **Appendix**).  
94 Also, solutions with high osmolality and/or very low or high pH cannot be administered  
95 through SC route due to the risk of cutaneous necrosis.<sup>19</sup> Reduced bioavailability (due  
96 to partial absorption) and potential underdosing are other relevant issues that should be  
97 considered when using the SC route.

98 - **Subcutaneous administration of antibiotics**

99 In some European countries, SC administration of antibiotics, although off-label,  
100 appears to be commonly considered by infectious diseases (ID) specialists and  
101 geriatricians.<sup>6, 27, 28, 29</sup> In a survey of 382 French practitioners, 96% of participants  
102 reported SC administration of antibiotics at some point, and more than a third of the  
103 geriatricians surveyed reported administering SC antibiotics at least weekly. Concerning  
104 the type of antibiotic, ID specialists and geriatricians reported previous use of SC route  
105 for ceftriaxone (100%), ertapenem (33%), teicoplanin (39%), aminoglycosides (35%),  
106 and amoxicillin (15%).<sup>6</sup> However, routine SC administration of antibiotics worldwide is  
107 infrequent.<sup>28, 29</sup>

108 **How is the subcutaneous route being used for the administration of antibiotics?**

109 Results from a prospective observational multicentric study that included 219 patients  
110 treated with SC antibiotics, showed that SC antibiotics are most frequently diluted in  
111 0.9% NaCl (72.3%), administered by slow injection; *i.e.*, > 5 min (61.3%), and using a  
112 flexible catheter (67.9%). The preferred injection sites were the thighs (51.7%) and  
113 flanks (25.1%). AEs were reported in 50 patients (22.8%), and included local pain  
114 (13.2%), induration (7.8%), hematoma (7.3%), and erythema (2.7%).<sup>27</sup> AEs were  
115 usually transient, and mainly reported with teicoplanin (70%). Administration of  
116 teicoplanin, and rapid injection (< 5 min), were both predictors of AEs. Antiplatelet or  
117 anticoagulant agents were not associated with AEs.<sup>27</sup> However, the principal limits of  
118 this survey were the sample size, participation on voluntary basis, and uncontrolled  
119 design.

120 Based on our daily experience and available evidence, clinical recommendations  
121 include checking the injection site daily to identify any local AEs. Regarding an optimal  
122 dilution, there is no strong evidence or consensus, and we currently use the same  
123 dilution as for the IV route. Administration of antibiotics diluted in 50–100 mL of

124 solvent (NaCl 0.9% or glucose 5%) by slow injection (by gravity; 30–60 min) and the  
125 use of a flexible catheter seems to decrease the risk of local AEs. Flexible catheters may  
126 be either removed between infusions, considering a change of injection site at each  
127 administration or kept patent for 3–4 days. While thighs and flanks are the preferred  
128 sites of injection, the back may be considered to prevent catheter removal by an agitated  
129 patient. Surveillance of spillage and catheter misplacement are also important.<sup>30</sup>

### 130 **Which antibiotics?**

#### 131 - **Importance of pharmacokinetic/pharmacodynamic properties for SC antibiotic** 132 **administration**

133 The main PK/PD indices of antibiotics are: the minimum inhibitory concentration  
134 (MIC; minimum concentration of the antibiotic that inhibits bacterial growth), the  
135 minimal plasma or trough concentration ( $C_{min}$ ), the peak concentration ( $C_{max}$ ), time to  
136 reach  $C_{max}$  ( $T_{max}$ ), the length of time during which the concentration of the drug is  
137 greater than the MIC ( $T > MIC$ ), peak concentration divided by MIC ( $C_{max}/MIC$ ), and the  
138 ratio of the 24 h area under the time-concentration curve divided by the MIC  
139 (AUC/MIC).<sup>32, 33, 34</sup>

140 Normally, the progressive diffusion of a molecule from the SC space to the  
141 intravascular compartment is associated with a decrease in the peak plasma  
142 concentration (reduced  $C_{max}$ ) and a longer time to achieve it (increased  $T_{max}$ ), compared  
143 with intermittent IV administration. However, the area under the time-concentration  
144 curve may be similar to that obtained with the IV route if the dose is entirely absorbed,  
145 *i.e.*, if the SC bioavailability is close to 100% (**Figure 1**). Hence, the SC route may be  
146 associated with prolongation of the action of a drug, even though its terminal half-life is  
147 unchanged compared to IV route. The next sections of the article will focus on the  
148 available evidence that supports how the SC route may optimize the PK/PD parameters

149 of time-dependent antibiotics, like certain  $\beta$ -lactams. By contrast, SC administration is  
150 unlikely to optimize the PK/PD of concentration-dependent agents—e.g.  
151 aminoglycosides and fluoroquinolones—as their  $C_{max}$  would be decreased.<sup>35</sup> Findings of  
152 reports on SC administration of antibiotics are listed in **Appendix**, and summarised  
153 along with practical recommendations in **Table 1**. These recommendations are mainly  
154 based on PK/PD and safety data. An important consideration is the heterogeneity among  
155 studies in terms of design, objectives, populations, reports of AE, clinical, and PK data.

### 156 **Ceftriaxone**

157 Ceftriaxone is frequently administered SC in some European countries, possibly due to  
158 its spectrum, half-life, and previous marketing approval for SC route use until 2015.  
159 However, this route has been discouraged by the European Medicines Agency because  
160 of insufficient clinical data, so SC use is currently off-label.<sup>36</sup> Still, SC ceftriaxone is  
161 prescribed in settings such as hospitalization, ambulatory assistance and palliative  
162 care.<sup>27, 37, 38, 39, 40, 41, 42, 43</sup> SC administration of ceftriaxone is associated with a lower  
163 peak concentration compared to IV administration, but its bioavailability approaches  
164 100%.<sup>39</sup> Other PK parameters such as the trough level, AUC, and T>MIC (which is  
165 predictive of the efficacy of  $\beta$ -lactams), are adequate compared to the IV route.<sup>37, 38, 41, 42</sup>  
166 Moreover, co-administration of ceftriaxone with recombinant hyaluronidase is  
167 associated with a higher  $C_{max}$  and reduced  $T_{max}$ .<sup>39</sup> Ceftriaxone is generally well  
168 tolerated; the most frequently reported AE is pain at the injection site, which may be  
169 ameliorated by previous application of lidocaine or recombinant hyaluronidase.<sup>27, 37</sup>  
170 Rapid injection of ceftriaxone should be avoided as it increases pain.<sup>27, 38, 39</sup> The  
171 available evidence for the efficacy and tolerability of ceftriaxone by SC route could  
172 support its use.<sup>27, 38, 40, 42</sup> (**Appendix**).

### 173 **Ertapenem**

174 Ertapenem is mainly used to treat infections caused by Gram-negative bacteria that  
175 produce extended-spectrum  $\beta$ -lactamases (ESBL-E). SC administration of ertapenem  
176 has been studied, but its clinical use is off label. Frasca *et al.* reported that SC  
177 administration resulted in a lower  $C_{max}$  compared to IV administration, but the AUCs  
178 over the dosing interval were similar, which suggests a bioavailability close to 100%.<sup>44</sup>  
179 Similar findings have been reported for high-dose ertapenem in bone and joint  
180 infections (BJI).<sup>45, 46</sup> Population PK/PD parameters and the results of simulations  
181 suggest that SC ertapenem has a comparable T>MIC index respect to IV route.<sup>26</sup> In a  
182 recent study of older persons (mean age, 86 years) with mainly urinary or respiratory  
183 tract infections, SC and IV ertapenem presented no significant differences in individual  
184 AUCs or the chosen PTA (probability of target attainment ) of maintaining a  $fT>MIC$  at  
185 least 40% of the time.<sup>30</sup> Forestier *et al.* has also reported successful SC use of ertapenem  
186 for urinary tract infections caused by ESBL-E.<sup>47</sup>  
187 Studies mainly report mild AEs with SC use of ertapenem, excepting one report of skin  
188 necrosis.<sup>26, 30, 44, 46</sup> Therefore, SC administration of ertapenem could be considered as an  
189 alternative to IV administration. (Appendix).

190 - **Teicoplanin**

191 Teicoplanin is a glycopeptide used as an alternative to vancomycin for the treatment of  
192 infections caused by some Gram-positive bacteria. It has a long elimination half-life,  
193 and several days are necessary to achieve a steady-state concentration, which normally  
194 requires the use of loading doses during the first days of therapy.<sup>48, 49</sup> Four studies have  
195 evaluated the tolerance and efficacy of SC teicoplanin. The first assessed the efficacy,  
196 tolerance, and PK of teicoplanin delivered by SC and IV routes; PK results showed that  
197 the  $C_{min}$  did not differ between IV and SC routes during the first 14 days of treatment.<sup>50</sup>  
198 In the second study, the SC route was used after an initial IV loading. Wherein IV route

199 resulted in a higher peak concentration, the  $C_{min}$  was higher at 48 h after SC  
200 administration.<sup>25</sup> The third study, mainly comprised by older patients with BJI, showed  
201 that 85% of participants achieved the target  $C_{min}$  irrespective of the route of  
202 administration (IM, IV, or SC).<sup>51</sup> In addition, Cazaubon *et al.* showed that SC  
203 administration of teicoplanin was associated with a lower  $C_{min}$  and plasma concentration  
204 (AUC) after a 2-day loading phase, but these differences were absent after 14 days due  
205 to drug accumulation.<sup>52, 53</sup> SC teicoplanin has also been used to treat infective  
206 endocarditis, however this has only been anecdotal.<sup>54</sup>

207 The incidence of AEs after SC administration of teicoplanin ranges from 10% to 30%  
208 (mainly local pain). However, in the multicentric survey of Roubaud-Baudron *et al.*, SC  
209 teicoplanin was independently associated with AEs.<sup>27</sup> Similarly, El Samad *et al.* found  
210 that the frequency of SC teicoplanin-associated AEs increased for doses > 600 mg per  
211 day, suggesting that concentration could influence tolerance.<sup>25</sup> (**Appendix**).

## 212 - Aminoglycosides

213 Studies of SC administration of amikacin and tobramycin showed a lower  $C_{max}$ , higher  
214  $T_{max}$ , and comparable bioavailability respect to IV administration. However, these  
215 studies are outdated and have methodological limitations; hence, their relevance to  
216 current clinical practice is limited.<sup>55, 56, 57, 58</sup>  $C_{max}$  is an important PK parameter for these  
217 concentration-dependent antibiotics and SC route could decrease their efficacy.  
218 Amikacin, and gentamycin have poor local tolerability and a high rate of severe local  
219 AEs, including painful nodules, ulcers, and cutaneous necrosis.<sup>59, 60, 61, 62, 63</sup> Currently,  
220 aminoglycosides are rarely administered by SC route, and the available evidence does  
221 not support their use.<sup>7, 8, 9, 27</sup> (**Appendix**).

## 222 Other antibiotics

223 SC administration of ampicillin, cefepime, and temocillin present a similar PK profile to  
224 that of the other studied antibiotics, characterized by a delayed  $T_{max}$  but similar AUCs.<sup>55,</sup>  
225 <sup>64, 65</sup> However, these studies were performed in healthy volunteers and with single-dose  
226 PK analysis.

227 Some antibiotics—vancomycin, oxacillin, and cefuroxime—induce endothelial toxicity  
228 when administered IV, and may not be well tolerated when administered SC as their  
229 absorption would take place on interstitial vasculature.<sup>31</sup>

230

### 231 **When to perform SC administration?**

232 Current evidence shows that IV route represents the best option to initiate antibiotic  
233 therapy in severe infections (sepsis, septic shock), as therapeutic concentrations are  
234 rapidly achieved. However, switching from IV to SC once the patient has been  
235 stabilized is feasible, particularly for time-dependent antibiotics, provided that the  
236 AUCs and T>MIC values are comparable. In non-urgent situations, particularly when  
237 oral access is limited, initiating antibiotics by SC route could be discussed as an  
238 alternative.

239 Indications for SC administration of antibiotics are not standardized. In the previously  
240 described survey by Roubaud-Baudron *et al.* , in almost half the cases SC route was  
241 used as a switch from IV or oral routes.<sup>27</sup> Frequent reasons for SC administration were:  
242 poor venous access, palliative care, patient agitation, contraindications for oral and IM  
243 administration, and non-availability of a suitable oral antibiotic. Also, SC administration  
244 has been used to facilitate hospital discharge or prevent hospitalization.<sup>27, 29</sup>

245 Infections requiring prolonged antibiotic administration, usually managed in hospital  
246 (*e.g.*, BJI or infective endocarditis), could benefit from SC route due to its safety,  
247 potential suitability for ambulatory care, easy supervision, and its PK and PD properties.

248 SC administration could be particularly useful for people with poor venous access, such  
249 as older adults and IV drug users. It could also be a resource to consider in persons with  
250 hyperactive delirium, and to prevent functional decline, as it poses less of a restraint to  
251 mobility than continuous IV lines. SC administration of antibiotics may also be  
252 considered in special conditions, including patients with an altered mental state, patients  
253 with swallowing disorders, and those receiving palliative care. It is not infrequent that in  
254 those patients, central venous catheters or peripherally inserted central catheters (PICC)  
255 are placed, being inappropriate as they are uncomfortable, and increase the risk of  
256 further complications like thrombosis or infection.

257 - **Future perspectives regarding SC administration**

258 The interest in SC administration of drugs is increasing in many specialties, and for  
259 diverse agents.<sup>66</sup> Therefore, multiple strategies for optimizing the efficacy and tolerance  
260 of SC administration are under development, such as the use of recombinant human  
261 hyaluronidase to decrease the diffusion barrier.<sup>67, 68, 69, 70</sup> Also, interestingly, simple  
262 tools like mentholated warm compresses, may improve the SC blood flow rate and  
263 absorption of antibiotics.<sup>71</sup>

264 SC route may be a useful resource in the treatment of ambulatory patients in developing  
265 countries, as well as vulnerable patients (including IV drug users), people in remote  
266 locations and could also find applications in military medicine.

267 The absence of studies with clinical efficacy endpoints, adequate controls, large sample  
268 sizes, and the lack of analysis of PK/PD parameters limit the use of SC administration  
269 for most antibiotics. Still, studies focusing on PK/PD parameters and safety analysis of  
270 new routes for previously approved antibiotics may be appropriate for supporting (or



271 not) the use SC without necessarily conducting full comparative studies, as pointed in  
272 FDA guidelines and other publications.<sup>72, 73</sup>

273 Future studies should be conducted taking in account special populations (obese, older,  
274 and malnourished patients), antibiotics administered more than once daily, or in  
275 continuous infusion. They should also have an adequate modelling to limit the number  
276 of biologic samples taken from the population, and with parallel-group or crossover  
277 designs. Some current initiatives are already trying to address the main limitations.<sup>74</sup>

278 The potential advantages of SC administration of antibiotics must not override  
279 compliance with good clinical practices; particularly, avoidance of over-prescription  
280 and switching to a reduced-spectrum antibiotic once the results of drug susceptibility  
281 tests are available. Finally, daily inspection of the injection site is needed, as in all  
282 medical procedures that involve drug delivery.

### 283 **Conclusion and implications**

284 SC administration of antibiotics may be useful, reliable, economical, and easy to apply  
285 in various settings such as in-hospital care, long-term care facilities or ambulatory care.  
286 In some cases, the SC route for antibiotics may also be considered to facilitate hospital  
287 discharge in well selected patients. SC administration can optimize time above MIC but  
288 decreases  $C_{max}$ , hence “time dependent” antibiotics are probably the best candidates for  
289 this route. Further clinical studies are needed to assess the risks and benefits of SC  
290 administration in time-dependent antibiotics. Finally, SC administration should be  
291 considered during the development of new antimicrobial agents.

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511 ClinicalTrials.gov ID: NCT03583749

512 **Table 1. Summary of evidence and practical recommendations**

Drug Categories	Summary of Evidence	Recommendations for clinicians
<ul style="list-style-type: none"> <li>• <b>General considerations</b></li> </ul>	<ul style="list-style-type: none"> <li>- SC use of antibiotics is associated with (<i>versus</i> IV):               <ul style="list-style-type: none"> <li>○ <math>\downarrow C_{max}</math></li> <li>○ <math>\uparrow T_{max}</math></li> <li>○ Similar AUCs (considering total absorption of antibiotic dose)</li> <li>○ Similar T&gt;MIC.<sup>25-26, 30, 37-39, 41-42,44-45, 50, 52-53, 55-58</sup></li> </ul> </li> <li>- T&gt;MIC is critical for “time-dependant” antibiotics</li> <li>- <math>C_{max}/MIC</math> is critical for “concentration-dependant” antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>• SC route for time-dependent antibiotics like beta-lactams might be considered given their PK/PD properties. *</li> <li>• SC route for concentration-dependent antibiotics like aminoglycosides should not be used given their PK/PD properties and a poor safety profile. *</li> <li>• SC route might be considered after an initial IV loading phase, as IV remains the route for emergency. *</li> <li>• SC route is reasonable as an initial option in patients with non-severe infections or patients in which other routes are not feasible / desirable. #</li> <li>• The use of a flexible catheter, slow injection (&gt; 5 minutes), and daily surveillance of the device may decrease the risk of local AEs. †</li> <li>• Antibiotic dilution for SC or IV are the same †</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Cephalosporins</b></li> <li>• <b>Time-dependent antibiotics</b></li> <li>Ceftriaxone++</li> <li>Cefepime<sup>64</sup></li> <li>Ceftazidime<sup>71</sup></li> </ul>	<ul style="list-style-type: none"> <li>○ Most of the available evidence comes from SC ceftriaxone.</li> <li>○ Bioavailability ≈100%. Trough level, AUC, and T&gt;MIC are non-inferior to IV route.<sup>37-39, 41-42</sup></li> <li>○ Evidence from clinical use in hospitalization, ambulatory care, and palliative-care (including older population).<sup>6, 27, 29, 40, 42-43</sup></li> <li>○ Described as well tolerated, pain may be reduced by previous injection of lidocaine.<sup>37-40, 42, 43</sup></li> <li>○ Co-administration of SC antibiotics (ceftriaxone) with</li> </ul>	<ul style="list-style-type: none"> <li>• SC use of ceftriaxone might be considered (similar bioavailability compared to the IV route with a good safety profile) *</li> <li>• Other cephalosporins may be considered too but evidence is scarce. *</li> </ul>

	<p>recombinant hyaluronidase has been described to <math>\uparrow C_{max}</math> and <math>\downarrow T_{max}</math>.<sup>39</sup></p> <ul style="list-style-type: none"> <li>○ Approximate number of individuals having received SC cephalosporins within the revised studies: 438</li> </ul>	
<ul style="list-style-type: none"> <li>● <b>Carbapenems</b></li> <li>● <b>Time-dependent antibiotics</b></li> </ul> <p>Ertapenem</p>	<ul style="list-style-type: none"> <li>○ Ertapenem is the main carbapenem studied for SC use.</li> <li>○ Similar AUC, T&gt;MIC and PTA <i>versus</i> IV route.<sup>26, 30, 44-45</sup></li> <li>○ Clinical studies in hospitalized and ambulatory patients with ESBL-E infections (including older population).<sup>6, 27, 29, 30, 44, 47</sup></li> <li>○ Described as well tolerated, one reported case of skin necrosis.<sup>30, 27, 44, 45, 47</sup></li> <li>○ Approximate number of individuals having received SC Ertapenem within the revised studies: 174</li> </ul>	<ul style="list-style-type: none"> <li>○ SC use of ertapenem might be considered (similar bioavailability compared to the IV route with a good safety profile). *</li> </ul>
<ul style="list-style-type: none"> <li>● <b>Glycopeptides</b></li> <li>● <b>Time-dependent antibiotics</b></li> </ul> <p>Teicoplanin</p>	<ul style="list-style-type: none"> <li>○ <math>\uparrow</math> or = <math>C_{min}</math> after loading phases.<sup>25, 50, 52, 53</sup></li> <li>○ Clinical evidence for hospitalized and ambulatory patients with BJI, and anecdotal use for endocarditis.<sup>25, 27, 50, 52-54</sup></li> <li>○ <math>\uparrow</math> rate of AEs reported with teicoplanin in comparison with other SC antibiotics.<sup>25, 27, 50, 53-54</sup></li> <li>○ Approximate number of individuals having received SC Teicoplanin within the revised studies: 81</li> <li>○ Vancomycin is venotoxic</li> </ul>	<ul style="list-style-type: none"> <li>○ SC teicoplanin might be considered (similar bioavailability compared to the IV route with a good safety profile). *</li> <li>○ Vancomycin should not be used by SC route. †</li> </ul>
<ul style="list-style-type: none"> <li>● <b>Aminoglycosides</b></li> <li>● <b>Concentration dependent antibiotics</b></li> </ul> <p>Tobramycin<sup>55, 57</sup> Amikacin<sup>56</sup> Netilmicin<sup>58</sup> Gentamycin<sup>60-63</sup></p>	<ul style="list-style-type: none"> <li>○ <math>\downarrow C_{max}</math> and <math>\uparrow T_{max}</math>. Important caveat, as aminoglycosides are concentration-dependent antibiotics.</li> <li>○ Comparable, or difficult to interpret bioavailability respect to the IV route.<sup>55-58</sup></li> <li>○ Poor tolerability and diverse reports of cutaneous necrosis and painful ulcers.<sup>29, 55, 59-63</sup></li> </ul>	<ul style="list-style-type: none"> <li>○ SC aminoglycosides should not be performed (poor safety profile and inappropriate PK/PD data) *</li> </ul>

513 AE, adverse effects; AUC, area under the curve; BJI: bone-joint infection;  $C_{max}$ , peak concentration;  $C_{min}$ , minimal plasma concentration; ESBL,  
514 extended spectrum beta-lactamase; T>MIC, time for plasma concentration above the minimal inhibitory concentration; IV, intravenous; LOE: Level of

515 evidence; LTCF, long-term care facility; PD, pharmacodynamics; PK, pharmacokinetics; PTA, probability of target attainment; SC, subcutaneous;  $T_{max}$ ,  
516 time to peak concentration.

- 517 ○ \* Data derived from prospective studies (randomized, cross over or parallel groups)
- 518 ○ # Only case studies
- 519 ○ † Consensus of expert opinion based on clinical practice surveys

520

521

522 **Legends to Figures**

523 **Figure 1:** illustration of plasma concentration profile of drugs administered by intravenous (IV) and  
524 subcutaneous (SC) infusion.  $C_{max}$ , peak concentration;  $T_{max}$ , time to peak concentration; MIC,  
525 minimal inhibitory concentration.

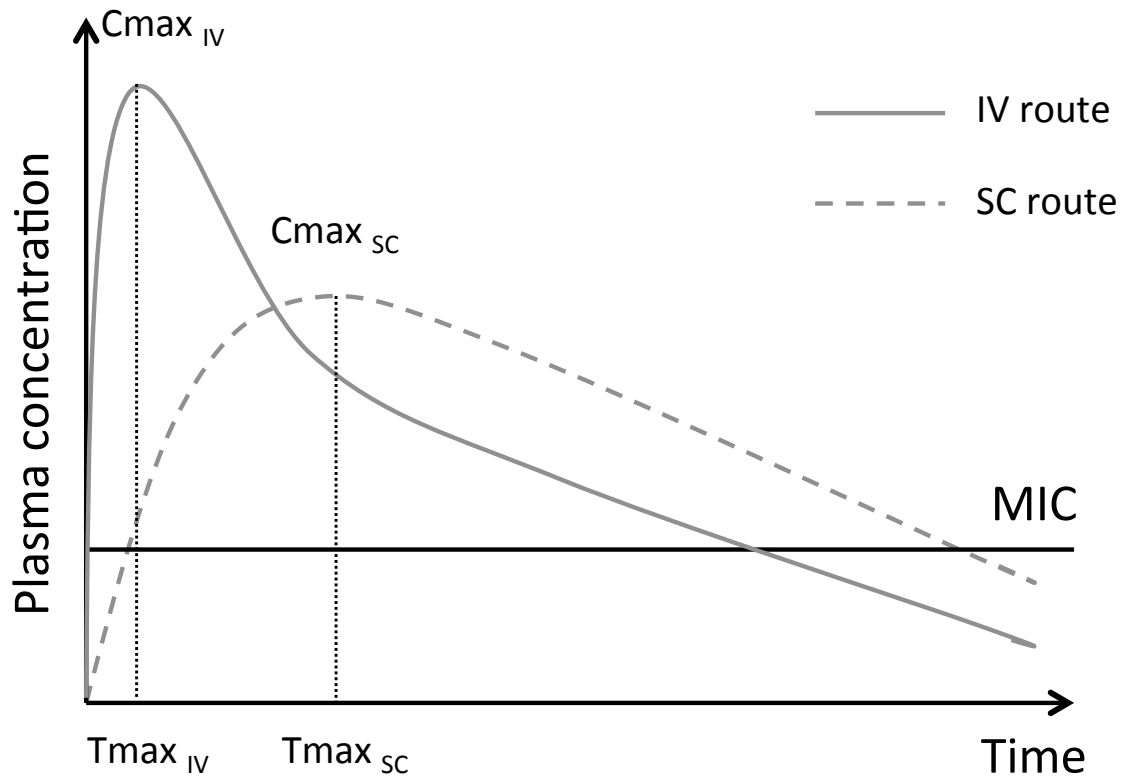


Figure 1.