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Review Article

Subcutaneous Antibiotic Therapy: The Why, How, Which Drugs and When



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

Design: Narrative review.

Setting and Participants: Hospitalized patients, persons in long-term care facilities and ambulatory care.

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

Results: Regarding tolerability, efficacy, and pharmacokinetic/pharmacodynamic profiles, most studies suggest that the SC route could be an alternative to the intravenous route, particularly for time-dependent antibiotics and among certain patient populations, such as patients with poor venous access, swallowing disorders, or behavioral disturbance. However, clinical evidence of the benefits and risks of SC antibiotic administration is still scarce and of low level.

Conclusions and Implications: SC administration of antibiotics may be useful in various settings such as in hospitalized patients and among those in long-term care facilities or being cared for at home. However, further clinical studies are needed to assess the pharmacokinetic/pharmacodynamic properties, as well as the risks and benefits of SC administration of antibiotics. In this review, we highlight the potential benefits of SC administration of antibiotics and address practical recommendations for its use. This information will enable improvement of treatment strategies and present the SC route as a potential option in specific situations.

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

In special populations such as older adults, an IV access may become challenging because of a poor peripheral venous network or agitation. IM access can be associated with pain and is contraindicated in patients receiving anticoagulants. Moreover, drugs administered through IM route can inadvertently be delivered to the subcutaneous (SC) space.^{2–5} Oral administration may be compromised by swallowing disorders, altered mental state, or by limited treatment options. In addition, the oral bioavailability of certain antibiotics may be reduced by food-drug, drug-drug interactions, and gastrointestinal disorders.^{2–4}

SC administration may help to circumvent those limitations frequently found in long-term care facilities, geriatric departments, palliative, and ambulatory care, which could partially explain why this route is mainly used in those settings.⁶ Nevertheless, SC administration of antibiotics is still off-label for many of them. An up-to-date review on this issue is needed, as a growing body of evidence could further support the use of the SC route.^{7–10} The main objectives of this review were to analyze the rationale for SC administration of antibiotics, make practical propositions to help clinicians in daily practice, as well as the development of future clinical trials.

Methods

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

Discussion

Why Subcutaneous Administration?

The SC route

Drugs administered by SC route are delivered into the interstitial space, a fibro-collagenous network beneath the dermis.¹¹ Following their delivery, one of the first things that influences absorption is molecular weight. Small molecules are absorbed into the interstitial vasculature by passive diffusion and endothelial permeability. Whereas high-molecular-weight agents are absorbed in the lymphatic system, which delays the time to achieve their maximum concentration.^{12,13} Other factors that influence the rate and extent of drug absorption are electric charge, hydrophilicity, degradation profile, and formulation (eg, concentration, volume, viscosity, and excipient profile).¹⁴ In clinical practice, the SC route is routinely used to administer vaccines, insulin, heparin, biological agents, and high-molecular-weight medications (eg, immunoglobulins).^{15,16}

Advantages of subcutaneous administration

The SC route may usefully combine some advantages of oral and other parenteral routes.^{17,18} SC administration of drugs is described as easy to perform (less demanding for nursing staff), it enables continuous administration of fluids (hypodermoclysis) or bolus administration of pharmacologic agents in diverse settings.^{19–22} Also, compared with IV routes, the risks of thrombosis and catheter infections in SC routes are less frequent or less severe; however, strong evidence from comparative studies is lacking.^{9,23} Unlike IM routes, SC administration is not contraindicated by anticoagulant therapy, which is common in older adults. In addition, the SC route has little impact on patient's mobility, which is a central component for the prevention of functional decline and rehabilitation.²⁴

Taking into account the mentioned profile, SC administration of antibiotics could find a place in hospital care or prolonged outpatient therapy, as well as in long-term care facilities.^{25,26}

Limitations of SC administration

Adverse events (AEs) caused by SC administration of drugs may include pain, edema, and inflammation at the injection site (details for AEs are described in the [Supplementary Table 1](#)). Also, solutions with high osmolality and/or very low or high pH cannot be administered through the SC route because of the risk of cutaneous necrosis.¹⁹ Reduced bioavailability (because of partial absorption) and potential underdosing are other relevant issues that should be considered when using the SC route.

SC administration of antibiotics

In some European countries, SC administration of antibiotics, although off-label, appears to be commonly considered by infectious disease specialists and geriatricians.^{6,27–29} In a survey of 382 French practitioners, 96% of participants reported SC administration of antibiotics at some point, and more than one-third of the geriatricians surveyed reported administering SC antibiotics at least weekly. Concerning the type of antibiotic, infectious disease specialists and geriatricians reported previous use of the SC route for ceftriaxone (100%), ertapenem (33%), teicoplanin (39%), aminoglycosides (35%), and amoxicillin (15%).⁶ However, routine SC administration of antibiotics worldwide is infrequent.^{28,29}

How is the SC Route being Used for the Administration of Antibiotics?

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

Based on our daily experience and available evidence, clinical recommendations include checking the injection site daily to identify any local AEs. Regarding an optimal dilution, there is no strong evidence or consensus and we currently use the same dilution as for the IV route. Administration of antibiotics diluted in 50–100 mL of solvent (NaCl 0.9% or glucose 5%) by slow injection (by gravity; 30–60 minutes) and the use of a flexible catheter seems to decrease the risk of local AEs. Flexible catheters may be either removed

between infusions, considering a change of injection site at each administration, or kept patent for 3–4 days. Although thighs and flanks are the preferred sites of injection, the back may be considered to prevent catheter removal by an agitated patient. Surveillance of spillage and catheter misplacement is also important.³⁰

Which Antibiotics?

Importance of pharmacokinetic/pharmacodynamic properties for SC antibiotic administration

The main pharmacokinetic/pharmacodynamic (PK/PD) indices of antibiotics are the minimum inhibitory concentration (MIC; minimum concentration of the antibiotic that inhibits bacterial growth), the minimal plasma or trough concentration (C_{min}), the peak concentration (C_{max}), time to reach C_{max} (T_{max}), the length of time during which the concentration of the drug is greater than the MIC ($T > MIC$), peak concentration divided by MIC (C_{max}/MIC), and the ratio of the 24-hour area under the time-concentration curve divided by the MIC (AUC/MIC).^{31–33}

Normally, the progressive diffusion of a molecule from the SC space to the intravascular compartment is associated with a decrease in the peak plasma concentration (reduced C_{max}) and a longer time to achieve it (increased T_{max}), compared with intermittent IV administration. However, the area under the time-concentration curve may be similar to that obtained with the IV route if the dose is entirely absorbed [ie, if the SC bioavailability is close to 100% (Figure 1)]. Hence, the SC route may be associated with prolongation of the action of a drug, even though its terminal half-life is unchanged compared with the IV route. The next sections of the article will focus on the available evidence that supports how the SC route may optimize the PK/PD parameters of time-dependent antibiotics, such as certain β -lactams. By contrast, SC administration is unlikely to optimize the PK/PD of the concentration-dependent agent (eg, aminoglycosides and fluoroquinolones) as their C_{max} would be decreased.³⁴ Findings of reports on SC administration of antibiotics are listed in the Supplementary Table 1 and summarized along with practical recommendations in Table 1. These recommendations are mainly based on PK/PD and safety data. An important consideration is the heterogeneity among studies in terms of design, objectives, populations, reports of AE, clinical, and PK data.

Ceftriaxone

Ceftriaxone is frequently administered by SC route in some European countries, possibly because of its spectrum, half-life, and previous marketing approval for SC route use until 2015. However, this route has been discouraged by the European Medicines Agency

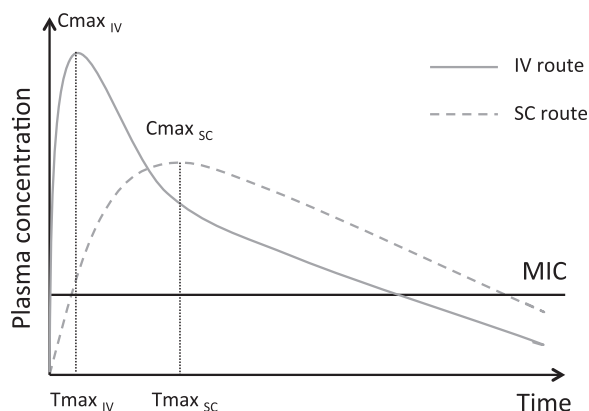


Fig. 1. Illustration of plasma concentration profile of drugs administered by IV and SC infusion.

because of insufficient clinical data; therefore, SC use is currently off-label.⁶⁰ Still, SC ceftriaxone is prescribed in settings such as hospitalization, ambulatory assistance, and palliative care.^{27,35–39,51,52} SC administration of ceftriaxone is associated with a lower peak concentration compared with IV administration, but its bioavailability approaches 100%.³⁷ Other PK parameters, such as the trough level, AUC, and $T > MIC$ (which is predictive of the efficacy of β -lactams), are adequate compared with the IV route.^{35,36,38,39} Moreover, co-administration of ceftriaxone with recombinant hyaluronidase is associated with a higher C_{max} and reduced T_{max} .³⁷ Ceftriaxone is generally well tolerated; the most frequently reported AE is pain at the injection site, which may be ameliorated by previous application of lidocaine or recombinant hyaluronidase.^{27,35} Rapid injection of ceftriaxone should be avoided as it increases pain.^{27,36,37} The available evidence for the efficacy and tolerability of ceftriaxone by SC route could support its use.^{27,36,39,51} (Supplementary Table 1).

Ertapenem

Ertapenem is mainly used to treat infections caused by Gram-negative bacteria that produce extended-spectrum β -lactamases. SC administration of ertapenem has been studied, but its clinical use is off label. Frasca et al reported that SC administration resulted in a lower C_{max} compared with IV administration, but the AUCs over the dosing interval were similar, which suggests a bioavailability close to 100%.⁴⁰ Similar findings have been reported for high-dose ertapenem in bone and joint infections (BJIs).^{41,61} Population PK/PD parameters and the results of simulations suggest that SC ertapenem has a comparable $T > MIC$ index with respect to IV route.²⁶ In a recent study of older persons (mean age, 86 years) with mainly urinary or respiratory tract infections, SC and IV ertapenem presented no significant differences in individual AUCs or the chosen probability of target attainment of maintaining an $fT > MIC$ at least 40% of the time.³⁰ Forestier et al have also reported successful SC use of ertapenem for urinary tract infections caused by extended-spectrum β -lactamases.⁵³

Studies mainly report mild AEs with SC use of ertapenem, excepting one report of skin necrosis.^{26,30,40,61} Therefore, SC administration of ertapenem could be considered as an alternative to IV administration (Supplementary Table 1).

Teicoplanin

Teicoplanin is a glycopeptide used as an alternative to vancomycin for the treatment of infections caused by some Gram-positive bacteria. It has a long elimination half-life, and several days are necessary to achieve a steady-state concentration, which normally requires the use of loading doses during the first days of therapy.^{62,63} Four studies have evaluated the tolerance and efficacy of SC teicoplanin. The first assessed the efficacy, tolerance, and PK of teicoplanin delivered by SC and IV routes; PK results showed that the C_{min} did not differ between IV and SC routes during the first 14 days of treatment.⁴² In the second study, the SC route was used after an initial IV loading. Wherein IV route resulted in a higher peak concentration, the C_{min} was higher at 48 hours after SC administration.²⁵ The third study, mainly composed of older patients with BJI, showed that 85% of participants achieved the target C_{min} irrespective of the route of administration (IM, IV, or SC).⁶⁴ In addition, Cazaubon et al showed that SC administration of teicoplanin was associated with a lower C_{min} and plasma concentration (AUC) after a 2-day loading phase, but these differences were absent after 14 days because of its drug accumulation.^{43,44} SC teicoplanin has also been used to treat infective endocarditis; however, this has only been anecdotal.⁵⁴

The incidence of AEs after SC administration of teicoplanin ranges from 10% to 30% (mainly local pain). However, in the multicentric survey of Roubaud-Baudron et al, SC teicoplanin was independently associated with AEs.²⁷ Similarly, El Samad et al found that the

Table 1
Summary of Evidence and Practical Recommendations

Drug Categories	Summary of Evidence	Recommendations for Clinicians
<ul style="list-style-type: none"> General considerations 	<ul style="list-style-type: none"> SC use of antibiotics is associated with (vs IV): ↓ C_{max} ↑ T_{max} Similar AUCs (considering total absorption of antibiotic dose) Similar $T > MIC$.^{25,26,30,35–48} $T > MIC$ is critical for “time-dependant” antibiotics C_{max}/MIC is critical for “concentration-dependent” antibiotics 	<ul style="list-style-type: none"> SC route for time-dependent antibiotics like beta-lactams might be considered given their PK/PD properties.* SC route for concentration-dependent antibiotics like aminoglycosides should not be used given their PK/PD properties and a poor safety profile.* SC route might be considered after an initial IV loading phase, as IV remains the route for emergency.* SC route is reasonable as an initial option in patients with non-severe infections or patients in which other routes are not feasible/desirable.† The use of a flexible catheter, slow injection (>5 min), and daily surveillance of the device may decrease the risk of local AEs.‡ Antibiotic dilution for SC or IV are the same‡
<ul style="list-style-type: none"> Cephalosporins Time-dependent antibiotics Ceftriaxone++ Cefepime⁴⁹ Ceftazidime⁵⁰ 	<ul style="list-style-type: none"> Most of the available evidence comes from SC ceftriaxone. Bioavailability ≈ 100%. Trough level, AUC, and $T > MIC$ are noninferior to IV route.^{35–39} Evidence from clinical use in hospitalization, ambulatory care, and palliative-care (including older population)^{6,27,29,39,51,52} Described as well tolerated, pain may be reduced by previous injection of lidocaine.^{35–37,39,51,52} Co-administration of SC antibiotics (ceftriaxone) with recombinant hyaluronidase has been described to ↑ C_{max} and ↓ T_{max}.³⁷ Approximate number of individuals having received SC cephalosporins within the revised studies: 438 	<ul style="list-style-type: none"> SC use of ceftriaxone might be considered (similar bioavailability compared with the IV route with a good safety profile)* Other cephalosporins may be considered too but evidence is scarce.*
<ul style="list-style-type: none"> Carbapenems Time-dependent antibiotics Ertapenem 	<ul style="list-style-type: none"> Ertapenem is the main carbapenem studied for SC use. Similar AUC, $T > MIC$, and PTA vs IV route.^{26,30,40,41} Clinical studies in hospitalized and ambulatory patients with ESBL-E infections (including older population)^{6,27,29,30,40,53} Described as well tolerated, one reported case of skin necrosis.^{27,30,40,41,53} Approximate number of individuals having received SC ertapenem within the revised studies: 174 	<p>SC use of ertapenem might be considered (similar bioavailability compared with the IV route with a good safety profile).*</p>
<ul style="list-style-type: none"> Glycopeptides Time-dependent antibiotics Teicoplanin 	<ul style="list-style-type: none"> ↑ or = C_{min} after loading phases.^{25,42–44} Clinical evidence for hospitalized and ambulatory patients with BJI, and anecdotal use for endocarditis.^{25,27,42–44,54} ↑ rate of AEs reported with teicoplanin in comparison with other SC antibiotics.^{25,27,42,44,54} Approximate number of individuals having received SC Teicoplanin within the revised studies: 81 Vancomycin is venotoxic 	<p>SC teicoplanin might be considered (similar bioavailability compared with the IV route with a good safety profile).*</p> <p>Vancomycin should not be used by SC route.†</p>
<ul style="list-style-type: none"> Aminoglycosides Concentration dependent antibiotics Tobramycin^{45,47} Amikacin⁴⁶ Netilmicin⁴⁸ Gentamycin^{55–58} 	<ul style="list-style-type: none"> ↓ C_{max} and ↑ T_{max}. Important caveat, as aminoglycosides are concentration-dependent antibiotics. Comparable, or difficult to interpret bioavailability respect to the IV route.^{45–48} Poor tolerability and diverse reports of cutaneous necrosis and painful ulcers.^{29,45,55–59} 	<p>SC aminoglycosides should not be performed (poor safety profile and inappropriate PK/PD data)*</p>

ESBL, extended spectrum beta-lactamase; LOE, level of evidence; LTCF, long-term care facility; PTA, probability of target attainment.

*Data derived from prospective studies (randomized, cross over or parallel groups)

†Only case studies

‡Consensus of expert opinion based on clinical practice surveys.

frequency of SC teicoplanin-associated AEs increased for doses >600 mg per day, suggesting that concentration could influence tolerance²⁵ (Supplementary Table 1).

Aminoglycosides

Studies of SC administration of amikacin and tobramycin showed a lower C_{max} , higher T_{max} , and comparable bioavailability with respect to IV administration. However, these studies are outdated and have methodological limitations; hence, their relevance to current clinical practice is limited.^{45–48} C_{max} is an important PK parameter for these concentration-dependent antibiotics and the SC route could decrease their efficacy. Amikacin and gentamycin have poor local tolerability and a high rate of severe local AEs, including painful nodules, ulcers, and cutaneous necrosis.^{55–59} Currently, aminoglycosides are rarely

administered by SC route, and the available evidence does not support their use.^{7–9,27} (Supplementary Table 1).

Other Antibiotics

SC administration of ampicillin, cefepime, and temocillin present a similar PK profile to that of the other studied antibiotics, characterized by a delayed T_{max} but similar AUCs.^{45,49,65} However, these studies were performed in healthy volunteers and with single-dose PK analysis.

Some antibiotics—vancomycin, oxacillin, and cefuroxime—induce endothelial toxicity when administered IV, and may not be well tolerated when administered by SC route, as their absorption would take place on interstitial vasculature.⁶⁶

When to Perform SC Administration?

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

Indications for SC administration of antibiotics are not standardized. In the previously described survey by Roubaud-Baudron et al, in almost one-half of the cases, the SC route was used as a switch from IV or oral routes.²⁷ Frequent reasons for SC administration were poor venous access, palliative care, patient agitation, contraindications for oral and IM administration, and nonavailability of a suitable oral antibiotic. Also, SC administration has been used to facilitate hospital discharge or prevent hospitalization.^{27,29}

Infections requiring prolonged antibiotic administration, usually managed in-hospital (eg, BJI or infective endocarditis), could benefit from the SC route because of its safety, potential suitability for ambulatory care, easy supervision, and its PK and PD properties.

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

Future perspectives regarding SC administration

The interest in SC administration of drugs is increasing in many specialties and for diverse agents.⁶⁷ Therefore, multiple strategies for optimizing the efficacy and tolerance of SC administration are underdevelopment, such as the use of recombinant human hyaluronidase to decrease the diffusion barrier.^{68–71} Also, interestingly, simple tools like mentholated warm compresses, may improve the SC blood flow rate and absorption of antibiotics.⁵⁰

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

The absence of studies with clinical efficacy endpoints, adequate controls, large sample sizes, and the lack of analysis of PK/PD parameters limit the use of SC administration for most antibiotics. Still, studies focusing on PK/PD parameters and safety analysis of new routes for previously approved antibiotics may be appropriate for supporting (or not) the use of SC administration without necessarily conducting full comparative studies, as pointed out in Food and Drug Administration guidelines and other publications.^{72,73}

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

The potential advantages of SC administration of antibiotics must not override compliance with good clinical practices; particularly, avoidance of overprescription and switching to a reduced-spectrum antibiotic once the results of drug susceptibility tests are available.

Finally, daily inspection of the injection site is needed, as in all medical procedures that involve drug delivery.

Conclusion and Implications

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

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Supplementary Table 1
Studies Describing SC Use of Antibiotics

Author, Year	Type of Study	Objective(s) of the Antibiotic	Population Characteristics	Adverse Events	Results
Muntendaum et al, 2016 ³⁸ ceftriaxone	Randomized, partially blinded, 3-period crossover study	<ul style="list-style-type: none"> • Noninferior SC antimicrobial coverage (time over MIC) when compared with the same dose given by IV infusion 	18 healthy male and female participants	Non reported	<p>PK results</p> <p>Ceftriaxone exposure following SC 2-h infusion of 1g was similar to that of the standard IV infusion over 30 min.</p> <ul style="list-style-type: none"> - Mean plasma concentrations after IV administration were comparable to concentrations reported in the package insert - The geometric mean absolute bioavailability following SC administration was 107.66% - Antimicrobial coverage (time over MIC) was equivalent with geometric mean ratio of 109.68%
Gauthier et al, 2014 ⁴⁰ ceftriaxone	Retrospective, single-center study	<ul style="list-style-type: none"> • To describe the SC administration of ceftriaxone in geriatric patients • To compare the profile of patients who received ceftriaxone SC to patients who received it IV • To compare the effectiveness of these 2 approaches for this population 	148 patients were included <ul style="list-style-type: none"> - IV (n = 110) - SC (n = 38) - Mean age: 84.7 ± 5.8 y 	No AE was documented related to the SC use of ceftriaxone in the medical or nursing records	<p>Clinical results</p> <ul style="list-style-type: none"> - Mean age was significantly higher in the SC group (86.9 ± 5.6 y) than in the IV group (83.9 ± 5.7 y, $P = .005$) - Dementia was more prevalent in the SC group (57% vs 25%, $P = .001$) - Patients in the SC group were more likely to be bedridden (22% vs 7% $P = .023$) and had a poorer functional status (higher ADL score; 7.79 vs 5.76, $P = .005$) - There was no significant difference in the bacteria isolated, site of infection, death rate, or cure rate
Harb et al, 2010 ³⁷ ceftriaxone	Phase 1, 2-part, placebo-controlled, crossover study <ul style="list-style-type: none"> - Part 1: placebo-controlled, single blind, concentration/dose escalation, safety and local tolerability study - Part 2: Randomized, placebo-controlled three-arm crossover study 	<ul style="list-style-type: none"> • To compare the PD and safety of recombinant human hyaluronidase (rHuPH20)-facilitated SC ceftriaxone administration vs SC ceftriaxone preceded by SC saline placebo or IV ceftriaxone administration 	54 healthy volunteers	At least one AE was experienced by 100% of participants after SC ceftriaxone, and by 76% after IV; the most commonly reported AEs were infusion-site reactions	<p>PK results</p> <ul style="list-style-type: none"> - The highest SC ceftriaxone concentration tested in part 1 (350/mL) was selected as the part 2 MTC - In part 2, median time to maximum concentration (T_{max}) was 1 h earlier ($P < .0001$), and C_{max} was 12% higher ($P < .0001$), for ceftriaxone (350 mg/mL) administered via rHuPH20-facilitated SC vs SC preceded by placebo - IV ceftriaxone led to higher C_{max} and shorter T_{max} values than either SC treatment - Ceftriaxone exposure (AUC) was comparable among all 3 treatments

Centeno et al, 2008 ⁵² ceftriaxone	Prospective	<ul style="list-style-type: none"> To evaluate the applicability and tolerability of SC ceftriaxone in palliative care patients 	<p>44 patients receiving hospital (n = 12) or domiciliary (n = 32) palliative care</p> <ul style="list-style-type: none"> Hospitalized patients received ceftriaxone for a median of 10 d (range: 2–16 d) Domiciliary patients received ceftriaxone for a median of 2.5 d (range: 1–10 d) 	<p>No reports of treatment suspension due to AEs</p> <p>Mild local AEs were present in 12 (5%) of the 224 SC administrations of antibiotics</p>	<p>Clinical results</p> <ul style="list-style-type: none"> SC administration of ceftriaxone could be used in palliative care patients
Melin-Coviaux et al, 2000 ³⁹ ceftriaxone	Prospective, randomized (open label)	<ul style="list-style-type: none"> To assess comparatively the efficacy, safety, and PK of ceftriaxone administered either SC or IV at a daily dose of 1 g/d 	<p>26 patients of a long-term care facility</p> <ul style="list-style-type: none"> Mean age: 82 y 	<p>Good general and local tolerability for both routes</p> <ul style="list-style-type: none"> Mild local and gastrointestinal AE were reported (self-limited) 	<p>PK results</p> <ul style="list-style-type: none"> Results show that ceftriaxone by IV and SC route are bioequivalent There were no differences in the studied PK parameters between the SC and IV routes (elimination half-life, plasmatic clearance, distribution volumes, or AUC)
Bricaire et al, 1988 ³⁶ ceftriaxone	Retrospective	<ul style="list-style-type: none"> To study the PK and tolerance of ceftriaxone by SC route 	<p>4 healthy volunteers</p> <ul style="list-style-type: none"> 2 women <p>8 patients (each patient being its own control)</p> <ul style="list-style-type: none"> Mean age: 67 y (19–88) 	<ul style="list-style-type: none"> Good general tolerability in healthy volunteers AE presented in all patients, pain being the most frequently reported One cases of SC necrosis was reported Ceftriaxone + 1% lidocaine was tolerable to all patients SC administration of 0.5 g of Ceftriaxone reported no intestinal side effects 	<p>PK results</p> <ul style="list-style-type: none"> Plasma concentrations of ceftriaxone obtained by SC route were close to those obtained by IV route Prolonged action of SC route was observed in comparison to IV route
Borner et al, 1985 ³⁵ ceftriaxone	Prospective, randomized cross-over study	<ul style="list-style-type: none"> To study the PK of ceftriaxone after SC and IV administration in healthy volunteers 	<p>10 healthy volunteers</p> <ul style="list-style-type: none"> 5 male, 5 female Age range: 22–43 y 	<ul style="list-style-type: none"> No severe antibiotic-related adverse effects were reported 	<p>PK results</p> <ul style="list-style-type: none"> Comparison of the PK parameters did not show relevant differences between IV and SC administration The bioavailability of SC administration was $0.96 \pm 0.26\%$
Roubaud-Baudron et al, 2019 ³⁰ ertapenem	Prospective, non-interventional analysis	<ul style="list-style-type: none"> Report and compare ertapenem PK data between IV and SC routes in older persons 	<p>Patients >65 y receiving ertapenem (1 g once daily) for at least 48 h (IV or SC, steady state) were prospectively enrolled</p> <p>26 patients</p> <ul style="list-style-type: none"> IV, n = 10 (mean age, 87 ± 7 y) SC, n = 16 (mean age, 88 ± 5 y) 	<ul style="list-style-type: none"> No severe antibiotic-related adverse effects were reported 	<p>PK results</p> <ul style="list-style-type: none"> The mean C_0 (immediately before the infusion) and $C_{2.5}$ (2 h after the end of the infusion) values were not significantly different between the IV and SC groups The mean $C_{0.5}$ (at the end of the infusion) was higher in the IV group compared with the SC group The mean individual AUCs for IV vs SC, and the other PK objectives chosen were not significantly different between groups
Goutelle et al, 2018 ²⁶ ertapenem	Retrospective analysis of PK data	<ul style="list-style-type: none"> To perform a population PK analysis and PK/PD simulation of ertapenem administered by the IV or SC route to patients with BJI 	<p>31 patients (mean age, 58 ± 16 y)</p> <p>46 PK profiles (IV, n = 13; SC, n = 33)</p> <p>133 antibiotic concentrations available for modelling</p>	<p>None reported</p>	<p>PK results</p> <ul style="list-style-type: none"> Twice daily dosing, SC route, and renal impairment were associated with an increased probability to achieve the PK/PD objective

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Supplementary Table 1 (continued)

Author, Year	Type of Study	Objective(s) of the Antibiotic	Population Characteristics	Adverse Events	Results
Ferry et al, 2012 ⁴¹ ertapenem	Retrospective, single-center study	<ul style="list-style-type: none"> Evaluate the safety, efficacy, and PK parameters of ertapenem administered by the IV or SC route as salvage therapy in difficult-to-treat BJI Compare, C_0, C_{max}, and C_{6h} obtained by the SC vs IV route Focus on SC data to estimate the $t_{1/2}$ and AUC	17 patients <ul style="list-style-type: none"> Mean age, 59 ± 17 y 3 patients received only IV injections 4 patients received IV or SC injections 10 patients received SC injections Mean treatment duration, 90 ± 38 d 	One patient experienced a serious AE (encephalopathy) <ul style="list-style-type: none"> No serious local AEs 	PK results <ul style="list-style-type: none"> The C_0 was higher in patients receiving ertapenem SC, whereas the C_{max} was lower Focusing on the results from the 14 patients who received ertapenem by the SC route, the median estimated apparent $t_{1/2}$ was 5.9 h, whereas the known $t_{1/2}$ after IV injection is 3.8 h. The estimated ertapenem AUC between 2 SC injections (every 12 h) was similar to that between 2 IV injections (every 24 h)
Forestier et al, 2012 ⁵³ ertapenem	Retrospective single center	<ul style="list-style-type: none"> To describe the experience of utilization of ertapenem by the IV or SC route for the treatment of UTI caused by ESBL-producing <i>Enterobacteriaceae</i> (ESBL-E) 	25 patients <ul style="list-style-type: none"> Mean age, 66.4 ± 16.5 y SC administration of ertapenem: 20 patients (80%) Outpatient parenteral antibiotic therapy: 23 patients (92%) 2 or more risk factors for a UTI per patient: 14 (66%) 	One case (4%) of localized skin necrosis was reported in the SC group (required local treatment)	Clinical results <ul style="list-style-type: none"> All patients showed clinical resolution of the infection at the end of antibiotic treatment At the end of treatment, the urine samples of 12 patients were sterile Three mo after the end of treatment, 5 patients had relapsed and 6 developed a UTI caused by another bacterium (no difference between routes)
Frasca et al, 2010 ⁴⁰ ertapenem	Prospective	<ul style="list-style-type: none"> To compare the PK of ertapenem at steady state following 30 min IV and SC infusions 	6 patients (early onset ventilator-associated pneumonia (n = 5) and surgical wound infection (n = 1) <ul style="list-style-type: none"> Mean age, 56 ± 19 y 	No local or systemic AE	PK results <ul style="list-style-type: none"> Ertapenem plasma concentration-time showed a 3-fold reduction in C_{max} and 5-fold increase in T_{max} after SC infusion compared with IV The AUCs of the 2 routes were identical
Cazaubon et al, 2017 ⁴³ teicoplanin	Retrospective analysis of PK data	<ul style="list-style-type: none"> To perform a population PK data analysis of teicoplanin administered by the SC and IV routes To identify the optimal loading dose regimens of teicoplanin in terms of efficacy and prevention of resistance 	98 patients <ul style="list-style-type: none"> ICU group (n = 12), geriatric group (n = 86) Infections caused by Gram-positive cocci 862 antibiotic concentrations available for PK modelling	None reported	PK results <ul style="list-style-type: none"> The SC route was associated with a lower initial C_{min} and AUC compared with the IV route. The difference disappeared after 14 d for all tested doses of antibiotic.
Peeters et al, 2016 ⁴² teicoplanin	Retrospective single-center cohort study	<ul style="list-style-type: none"> To assess the efficacy and tolerance of teicoplanin for <i>S. aureus</i> BJI, focusing on SC use. 	65 patients <ul style="list-style-type: none"> Median age, 62 y (IQR, 48–75 y) IV route (n = 51, 78.5%) SC route (n = 14, 21.5%) 30.8% native and 69.2% orthopedic device-related infections 	Incidence of AEs, 10%: <ul style="list-style-type: none"> Four by the IV route Two by the SC route All AEs resolved after medication withdrawal Maculopapular rash (pancytopenia in one case)	Clinical results <ul style="list-style-type: none"> SC and IV administration of teicoplanin showed no difference in tolerability PK results <ul style="list-style-type: none"> SC and IV administration of teicoplanin showed no difference in PK

El Samad et al, 2016 ²⁵ teicoplanin	Prospective open label	<ul style="list-style-type: none"> To determine the tolerability at the injection site of SC teicoplanin for the treatment of BJI To analyze the usefulness of teicoplanin for maintaining C_{min} within the therapeutic range 	30 patients enrolled (25 finished the study) <ul style="list-style-type: none"> Mean age, 62.4 y (range: 24–89 y) Mean estimated GFR creatinine clearance by MDRD formula: 108.6 mL/min 	No severe local AE, no related antibiotic discontinuation. Pain, 30%. Neutropenia, n = 2	<p>Clinical results</p> <ul style="list-style-type: none"> Good tolerability of SC administration of teicoplanin for the management of BJI caused by multiresistant Gram-positive cocci <p>PK results</p> <ul style="list-style-type: none"> IV administration of teicoplanin resulted in higher peak concentrations compared with the SC route, but higher trough concentrations were obtained using the SC route
Carpentier et al, 2013 ⁵⁴ teicoplanin	Case report	<ul style="list-style-type: none"> To report the use of SC teicoplanin in 2 children hospitalized in a pediatric cardiology service 	<p>Case 1: 5 y/o boy with infectious endocarditis associated with prosthetic material. After initial IV treatment, SC teicoplanin was applied for 8 weeks in association with rifampicin and netilmicin <i>per os</i></p> <p>Case 2: 11-y-old boy with infectious endocarditis after a Ross procedure (pulmonary autograft for correction of a bicuspid aortic valve). SC teicoplanin in association with rifampicin <i>per os</i> was used during the postoperative period after initial IV treatment</p>	No specific AE related to the treatment was reported	<p>Clinical results</p> <ul style="list-style-type: none"> SC administration of teicoplanin could be used for prolonged antibiotic therapy for infectious endocarditis in children after initial IV treatment
Barbot et al, 2003 ⁴⁴ teicoplanin	Prospective, randomized crossover study	<ul style="list-style-type: none"> To compare the PK parameters of sequential IV and SC teicoplanin in the plasma of patients in the surgical intensive care unit 	12 patients with suspected nosocomial infection <ul style="list-style-type: none"> antibiotic was first administered IV as loading dose On d 4 patients were randomized into 2 groups according to the results of PK studies 	Only 1 patient developed pain and erythema at the cutaneous injection site (sterile water was used instead of saline)	<p>PK results</p> <ul style="list-style-type: none"> Compared with a 30-min IV infusion, the peak concentration of teicoplanin after 30 min SC administration occurred later (median, 7 h, range: 5–18 h) and was lower Despite inter individual differences, no significant difference between SC and IV administration was observed in the trough antibiotic concentration or other PK parameters evaluated
Champoux et al, 1996 ⁴⁵ tobramycin, ampicillin	Retrospective	<ul style="list-style-type: none"> Comparison of the PK of tobramycin and ampicillin given by the SC vs IV routes in healthy volunteers 	<p>Tobramycin</p> <ul style="list-style-type: none"> 10 young volunteers (<50 y old) 10 older volunteers (>65 y old) <p>Ampicillin</p> <ul style="list-style-type: none"> 12 young volunteers (<50 y old) 10 older volunteers (>65 y old) 	Good general tolerability was described for both routes and antibiotics	<p>PK results</p> <ul style="list-style-type: none"> Compared to the IV route, the SC route delayed the time to reach T_{max} of tobramycin and ampicillin in both groups Plasma concentration of tobramycin at 30 min after infusion was lower by the SC than the IV route in both groups For tobramycin, the AUC of the SC route was slightly smaller than that of the IV route For ampicillin, the AUC of the SC route was greater than that of the IV route, for both groups Plasma concentrations of SC ampicillin at 30 min after the infusion were higher than those after IV administration in both groups

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Supplementary Table 1 (continued)

Author, Year	Type of Study	Objective(s) of the Antibiotic	Population Characteristics	Adverse Events	Results
Courcol et al, 1986 ⁴⁸ netilmicin	Retrospective	<ul style="list-style-type: none"> Report PK data during a preliminary study of tolerance to a single daily dose of SC aminoglycosides 	20 patients who had surgery for endocarditis <ul style="list-style-type: none"> 4 groups of 5 patients were constituted, according to criteria of obesity and number of daily SC injections (1 or 2) 	Not mentioned	PK results <ul style="list-style-type: none"> With a single injection, C_{max} and time to peak level appeared half an hour later respect to IV route PK data were not statistically different between normal-weighted and overweight patients for the SC route patients (peak and through, serum peak time, half-life and AUC)
Leng et al, 1979 ⁴⁶ Amikacin	Retrospective	<ul style="list-style-type: none"> Determine and compare the PK of amikacin by the IV, IM, and SC routes in healthy volunteers 	5 healthy volunteers <ul style="list-style-type: none"> Age range: 20–45 y 	Not mentioned	PK results <ul style="list-style-type: none"> Compared to the IV and IM route, the SC route delayed T_{max} Other established PK parameters after IV, IM and SC injection are difficult to interpret because different doses of amikacin were used
Babinet et al, 1976 ⁴⁷ Tobramycin	Retrospective	<ul style="list-style-type: none"> Describe the PK of tobramycin by the IM or SC route 	73 patients <ul style="list-style-type: none"> 46 IM patients 27 SC patients 	Not mentioned	Clinical results <ul style="list-style-type: none"> The obtained C_{max} was lower for patients receiving tobramycin by SC route
Matzneller et al, 2017 ⁶⁵ temocillin	Single-center study	<ul style="list-style-type: none"> Describe PK of temocillin in plasma, muscle and subcutis of healthy volunteers. 	8 male healthy volunteers <ul style="list-style-type: none"> Mean age 32.9 ± 12.1 y 	AE reported were of mild intensity and limited to the time of infusion: <ul style="list-style-type: none"> Burning sensation (50%) Pain (25%) Heat sensation (12.5%) One case of hypoesthesia (mild, duration of five mo) and tenderness (mild, duration three mo) were described 	PK results <ul style="list-style-type: none"> Compared to IV, SC dosing produced a slower and less pronounced increase of total temocillin in plasma, compensated by sustained drug levels over time The AUC_{0-12h} of temocillin after SC dosing corresponded to $86.6 \pm 10.0\%$ (range 70.1–100.9%) of the value after IV administration. Subcutis showed a slightly higher exposure to unbound temocillin compared with muscle, calculated by AUC_{0-12h})
Walker et al, 2005 ⁴⁹ cefepime	Prospective, single-center study	<ul style="list-style-type: none"> To determine the single-dose PK and tolerability of cefepime administered as an SC infusion in healthy volunteers and compare the profile respect IM route 	10 healthy volunteers <ul style="list-style-type: none"> 6 men, 4 women Age range: 18–65 y (median, 27 y) 	No AEs were reported	PK results <ul style="list-style-type: none"> Single-dose SC administration of cefepime resulted in a plasma concentration profile similar to single-dose IM administration
Noriega et al, 2018 ²⁹ ceftriaxone, amikacin, and ertapenem	Retrospective, single center	<ul style="list-style-type: none"> To describe experience with SC administration of antibiotics 	368 patients (71% with cognitive impairment) Mean age, 86.5 ± 6.5 y	Three percent of the study population Main AEs: edema and erythema Majority of AEs associated with amikacin	Clinical results <ul style="list-style-type: none"> SC injections, 2,446 Ceftriaxone (64%) Ertapenem (26%) Amikacin (10%) Mean duration of treatment: 6.15 ± 3.75 d Clinical resolution rate 82%

Roubaud-Baudron et al, 2017 ²⁷	Prospective observational multicenter study (France, 50 Infectious Diseases and Geriatric Departments)	<ul style="list-style-type: none"> To determine the tolerability of SC administration of antibiotics 	219 patients - Mean age, 83 ± 12.5 y	Reported in 50 patients (22.8%) The majority of cases were of mild local AEs (90%) - Pain (n = 29) - Induration (n = 17) - Hematoma (n = 16) Systemic AEs reported in five patients (2 severe)	Clinical results - Ceftriaxone (n = 163, 74.4%) and ertapenem n = 30, 13.7%) were the most frequently prescribed antibiotics - Principal causes for the SC route were poor venous access (65.3%) and palliative care (32.4%) - The class of antibiotic, especially teicoplanin (P = .002) and use of a rigid catheter (P = .009) were independently associated with AEs
Ebihara et al, 2016 ⁵⁰ ceftazidime	Prospective	<ul style="list-style-type: none"> To investigate the subcutaneous blood flow rate (SBFR) in healthy volunteers and patients with severe motor and intellectual disabilities (SMID) Evaluate the effect of mentholated warm compresses on SBFR and subcutaneous ceftazidime absorption in healthy volunteers 	41 healthy volunteers - 25 females, 16 males - Mean age, 45.7 ± 1.3 y - Age range: 21–58 y 48 patients with SMID - 25 females, 23 males - Mean age, 45.9 ± 12.8 y - Age range: 22–70 y Significant between-group differences in height, weight, and body mass index in both sexes (P < .001 for each comparison)	None reported	Clinical results - The SBFR was significantly lower in female patients with SMID than in female volunteers (P < .001) - No significant between-group difference in SBFR at any site in males - Application of mentholated warm compresses increased the SBFR 1.3–2.0-fold compared with baseline in the healthy controls
Forestier et al, 2015 ⁶	Retrospective, survey	<ul style="list-style-type: none"> To explore antibiotic administration by the SC route among French ID and geriatric healthcare practitioner 	382 practitioners completed the survey ID, n = 93; geriatricians, n = 289 (48% acute care, 52% rehabilitation care centers, nursing homes, and/or LTCF)	Pain was the main AE reported - "Sometimes", n = 225 (61.3%) - Often, n = 45 (9.5%) Skin necrosis - Recorded "sometimes" by 47 (12.8%) practitioners Lack of efficacy - Recorded "sometimes" by 73 (19.9%) practitioners	- 367 (96.1%) practitioners use the SC route to administer antibiotics - Ceftriaxone was the most frequently prescribed antibiotic. Of the practitioners that used the SC route, all but one had prescribed ceftriaxone - The SC route was used mainly in cases of unavailable oral, IV or IM routes, especially during palliative care

ADL, activities of daily living; ESBL, extended spectrum beta-lactamase; $\text{fT} > \text{MIC}$, time for free plasma concentration above the minimal inhibitory concentration; ICU, intensive care unit; IQR, interquartile range; LTCF, long-term care facility; MDR, multidrug resistant; MDRD, modification of diet in renal disease formula; MRSA, methicillin-resistant *S. aureus*; PTA, probability of target attainment; SIRS, systemic inflammatory response syndrome; UTI, urinary tract infection.