Review Article

Effectiveness of Subcutaneous Administration of Antibiotics to Control Infections in Elder Palliative Patients: A Systematic Review

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Abstract

Background: Infections are common in patients with advanced illnesses for whom the intravenous or oral route is not possible. The subcutaneous administration of antibiotics is a promising alternative, but there is not enough theoretical support for its use. This study aims to explore the effectiveness and safety of subcutaneous antibiotic therapy in the context of palliative care in elderly patients. **Methods**: A systematic review was conducted using PubMed and Embase, without time or language limits. Seven articles were selected on the effectiveness of subcutaneous antibiotic therapy in adult patients with chronic progressive diseases. The quality of the articles was assessed with the Newcastle Ottawa Scale and relevant data was extracted using a selection capture file. **Results**: Seven quasi-experimental studies evaluated 865 elderly patients with advanced diseases, comorbidities, and infections (ie, urinary tract, respiratory system, and bone joint) who received subcutaneous antibiotic therapy (ie, Ceftriaxone, Ertapenem, and Teicoplanin). The pooled success rate of subcutaneous antibiotics for the 7 studies was 71%, the therapy failure rate was 22%, its withdrawal mean was 8%, and the mean mortality rate was 7%. The studies were of low quality and were heterogeneous in the types of infections, types of antibiotics, time of follow-up, and outcomes assessed. **Conclusions**: Pilot studies have found a limited number of antibiotics that can be safely used to treat specific infections. Nevertheless, the data isn´t robust enough to recommend their use.

Keywords

subcutaneous, administration, antibiotics, palliative care, elderly, systematic review

Introduction

Worldwide approximately 68.9% of patients with non-communicable diseases benefit from palliative care.[1] The main pathologies are dementia (87%), lung diseases (73%), cerebrovascular diseases (66%), and malnutrition (65%).[1] However, patients with other diseases may also benefit from this discipline, especially when the curative treatment is determined to be ineffective, and palliative care is considered to attempt to provide the best quality of life possible.[2–5] Infections are among the most common complications and may lead to challenging decisions in end-of-life patients.[6,7] This is due to susceptibility to infections because of immunosuppression, compromised physiological barriers, pharmacological treatment's side effects and/or functional impairments. Infectious processes tend to increase the burden of symptoms of multiple comorbidities, impacting the quality of life of palliative patients and frequently becoming terminal events.[6,8,9]

Diagnosing infections in patients undergoing palliative care can be difficult due to comorbidities, unclear clinical manifestations, polypharmacy, and communication issues.[10,11] The most prevalent infections occur in the urinary, respiratory, tegumentary, and hematological systems.[12,13] Additionally, patients and their families may incorrectly perceive antibiotics as benign or less burdensome

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compared to other potentially life-prolonging interventions; For these reasons, preferences regarding antimicrobial therapy are rarely discussed (45.3%).[14-16] Antimicrobial use at end of life is common next to death (90%) and tends to be one of the last interventions to be withdrawn or withheld.[17,18] The goal of increased survival should be weighed against the risk of prolonging suffering in patients with advanced diseases.[14,18]

The subcutaneous (SC) route is a promising alternative to antibiotic therapy.[19-21] However, its use does not have solid theoretical support as highlighted by several systematic reviews.[22-25] There is a paucity of data about the capacity to achieve the needed antibiotic concentration at the site of infection through the subcutaneous route.[6,26] In palliative care, measuring antibiotic effectiveness includes other aspects such as comfort measures, and not only infection eradication or prevention.[27] The approach to the use of antibiotic therapy in terminal patients should be made by a multidisciplinary team through an individualized assessment, considering risks of adverse side effects (which might be devastating due to the underlying frailty and polypharmacy of these patients) and potential benefits, through advanced care planning and shared decision making in end of life.[14,18] This is why further research is needed to improve decision-making and define clear objectives of antibiotic therapies at the end of life.[26,28] Our study aims to explore the effectiveness of subcutaneous antibiotic therapy in the context of palliative care in elderly patients.

Materials and Methods

A systematic review was performed according to the reporting guidelines for systematic reviews and meta-analyses (PRISMA),[29] to obtain an overview of the medical literature, up to the 20th of September 2019, on the effectiveness of subcutaneous antibiotic therapy in elder patients under palliative care using the PubMed and Embase search engines. In addition, a manual search of articles and a selection of potentially relevant citations of the studies obtained in the systematic search were carried out. The preview of the systematic review is registered in PROSPERO - International prospective register of systematic reviews, with the identification number CRD42020160206.

Study Question and Objectives

The research question was: What is the effectiveness of subcutaneous antimicrobial administration for infection control in elder patients under palliative care? Developed under the components of PICO; P: Elder patient in palliative care, I: Antibiotic therapy by subcutaneous route, C: No comparison or administration of antibiotic by other routes, and O: Effectiveness of subcutaneous antibiotic therapy.

Eligibility Criteria

Articles were considered eligible if they met all the inclusion criteria: randomized controlled clinical trials or observational studies; adults with a chronic progressive disease; infection treated with subcutaneous antibiotic therapy; and report its effectiveness. Given the heterogeneity of the studies to report the effectiveness of the therapy or the advanced stage of the disease, a single criterion was not established for these variables, but it was requested that the study reported a method for this purpose. The search time and the language of the studies were not restricted. Articles whose objective was to report the pharmacokinetics of subcutaneous antibiotic therapy were excluded.

Search

The search strategy is specified in Table 1 and consists of the summary of #1 AND #2 AND #3 AND #4 for each database.

Quality of the Selected Articles

The quality of the selected articles was assessed with the Newcastle Ottawa Scale. This method values the quality of the selected observational articles and consists of 9 items grouped into 4 sections (Selection, Comparability, Outcome, and Statistics) that are relevant to the quality of an observational study. For each outcome of interest, validity scores were evaluated as follows: ≤5, low quality; 6-7, medium quality; 8-9, high quality.

Data Extraction and Synthesis

Selection criteria according to title and text abstract were applied independently by 2 investigators. Articles with no abstract available were selected based on the title. Subsequently, the results were compared and unified the list of articles for complete review. The following data were extracted and recorded in a duplicate format: title, characteristics of the participants, sample size, type of antibiotic used, dose, route of administration, comparison intervention (if any), possible biases, funding, and conflicts of interest. Disagreement between investigators was resolved by discussion. When no agreement could be reached, a third investigator was consulted. The selection process was documented in a selection capture file. The included studies are characterized by considerable heterogeneity that doesn't allow for statistical analysis, for which a narrative synthesis was performed.

Results

A total of 4374 records were retrieved from PubMed and Embase and 5 additional records were identified through other sources. After the exclusion of duplicates and the screening of

the articles by title and abstract; 22 articles were assessed for eligibility, from which 15 were excluded, including 7 studies that met all the criteria (Figure 1).

Characterization of the Population

The studies' population were elder patients with a mean age of 75 years[30-33] with multiple comorbidities as neurological, cardiovascular, respiratory, renal, gastrointestinal, endocrinological, immunological, hematological, psychiatric, and neoplastic diseases,[34,35] as well as high dependence, shown by the modified Charlson's comorbidity index,[32,33] WHO score,[32] Katz autonomy scale[32] and Barthel index.[31] Other factors used to identify palliative patients were not being candidate to optimal treatment due to underlying conditions,[31,33-35] poor 10-year survival prognosis,[32,33] and high functional dependence.[31,32] The gender distribution of the studies varied between

Table 1. PubMed and Embase Search Strategy.

Care, Palliative OR Palliative Treatment OR Palliative Treatments OR Treatment, Palliative OR Treatments, Palliative OR Therapy, Palliative OR Palliative Therapy OR Palliative Supportive Care OR Supportive Care, Palliative OR Palliative Surgery OR Surgery, Palliative
Subcutaneous Absorption OR Infusions, Subcutaneous OR Subcutaneous Tissue OR Hypodermoclysis OR subcutaneously OR subcutaneous OR administration, Subcutaneous
Frail Older Adults OR Adult, Frail Older OR Older Adult OR Older Adults, Frail OR Elderly, Frail OR Frail Elderly OR Elderly, Frail OR Frail Elders OR Assessment, Geriatric OR Assessments, Geriatric OR Geriatrics OR Geriatric
Antibiotic OR antibiotics OR antibiotic therapy OR antibiotic treatment

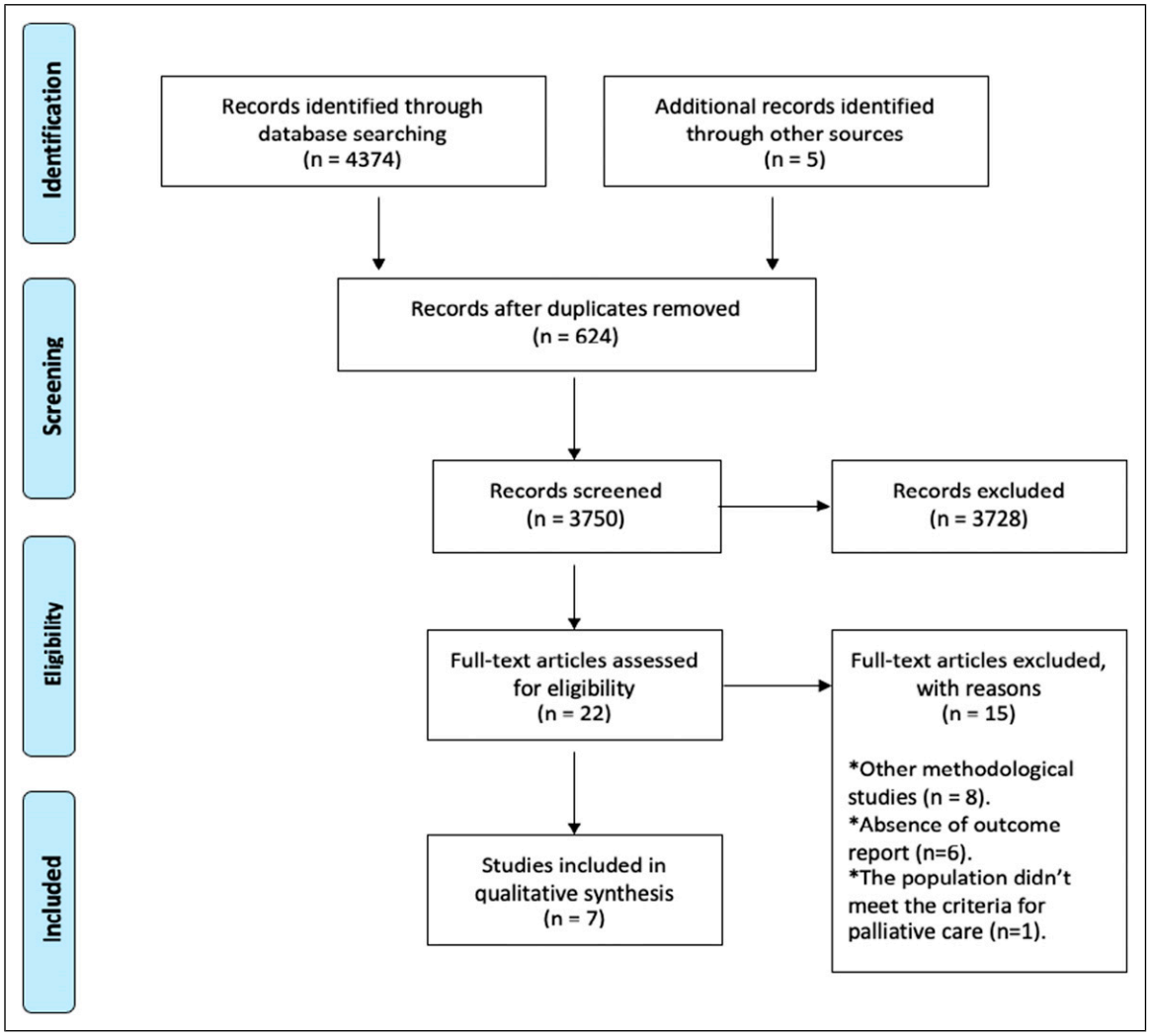

Figure 1. PRISMA flow-diagram.

Table 2. Population Characteristics of Included Studies.

		Eligibility Criteria			Population				Infection					
		Inclusion												
Author (s)	Follow -up (months)	Microorganism	Antiobiotic	Other	Patients (#)	Mean Age (years)	Gender (%) Male/Female	Comorbidities (%)	Microorganisms	Site/System	Sepsis State	SC Antibiotic Administration Indications	Functional or Prognostic Scales	Factors that Identify the Patient as Palliative
Pouderoux et al	96	Not reported	Ceftazidine, ceftiaxina and ertapenem SC PSAT.	Chronic ODI or CO.	10	79	(40/60)	Renal (40%) Hematological (20%) Neurological (10%)	*E. coli* (50%) S. ureus (40%)	*ODI (70%) *CO (30%)	Not reported	Ci for oral route PRP PMI Rams	Not reported	Elder population Comorbidities Not optimal treatment available
Forestier et al	27	Not reported	Ertapenem (IV or SC)	First episode of UTI ESBL-producing Enterobacteriaceae	25	66	(52/48)	Endocrinological (24%) Renal (32%) Immunological (16%)	*E. coli* (96%) *K. pneumoniae* (4%)	Prostatitis (52%) Pyelonephritis (40%) Cystitis (8%)	Not reported	Difficult vn acc Facilitate hospital discharge	Not reported	Elder population Comorbidities
El Samad et al	27	GPB(1)	Treatment with SC teicoplanin	With BJI.	30	62	(70/30)	Not reported	MRCoNS (38%) MRSA (35%)	ODI (67%) BJI (33%)	Not reported	Not reported	Not reported	Mature population Not optimal treatment available
Peeters et al	23	*Staphylococcusaureus*	SC teicoplanin	With BJI.	60	62	(57/43)	Endocrinological (35%) Respiratory (25%) Immunological (22%) Cardiovascular (16%) Renal (15%) Neurological (10%) Neoplastic (10%) Gastrointestinal (3%) Hematological (2%)	MRSA (17%) PMI (26%)	BJI (31%) ODI (69%)	Not reported	Not reported	*Modified Charlson's comorbidity index (7.5)	Mature population Ccomorbidities Not optimal treatment available Poor 10-year survival prognosis
Gauthier et al	12	Not reported	Ceftriaxone (IV or SC) at lease ≥2 injections with 24-hour interval		148	85	(53/47)	Psychiatric (44%) Neurological (31%)	*E. coli* (22%) Group D strep. (7%)	Respiratory (37%) Urinary (26%) Digestive (16%) Integumentary (3%) Cardiovascular (2%)	Uncomplicated (66%) Severe (33%) Septic shock (5%)	Difficult vn acc Difficulty to maintain vn acc Risks of vn acc	WHO score (2.95) Katz autonomy scale (6.8) Charlson's comorbidity score (7.6)	Elder population Comorbidities Poor 10-year survival prognosis High functional dependence
Roubaud-Baudron et al	5	Not reported	Treated at least one day with SC antibiotics		219	83	(43/57)	-	-	Urinary (44%) Respiratory (33%) BJI (7%) Digestive (6%) Other (10%)	Severe (6%)	Ci for oral route Ci for IM route Difficult vn acc Difficulty to maintain vn acc Facilitate hospital discharge Not active oral antibiotic drug *PC* decision	Not reported	Elder population
Noriega et al	48	Not reported	Indication of SC antibiotic		368	87	(35/65)	CVD (100%) Psychiatric (72%) Endocrinological (31%) Renal diseases (25%) Neurological (24%) Respiratory (10%)	*E. coli* (56%) *K. pneumoniae* (16%)	Respiratory (48%) Urinary (43%) Digestive (6%) Other (3%)	Not reported	Ci for oral route Ci for IM route Difficult vn acc *PC* decision	Barthel Index (39.7)	Elder population Comorbidities Not optimal treatment available High functional dependence

SC: Subcutaneous; IV: Intravenous; PSAT: Prolonged suppressive antibiotic therapy; CO: Chronic osteomyelitis; BJI: Bone joint infection; ODI: orthopedic device-related infection; ESBLs: Extended Spectrum Beta-Lactamases; MRSA: Methicillin-resistant *Staphylococcus aureus*; MRCoNS: Methicillin-resistant coagulase-negative staphylococci; UI: Urinary Infection, Mature adults 55-64 years old, Elder adults ≥65 years old; CVD: cardiovascular disease; *PC*: palliative care; Vn: vein acc:access; Ci: containdication; PRP: Pathogen's resistance profile; PMI: Polymicrobial infection. rams: History of drugrelated adverse events. 1: Gram positive bacteria susceptible to teicoplanin and resistant to betalactams, lincosamides, and quinolones, or allergic to penicillin or rifampin.

principally female[30,35] and mainly male.[32-34,36] For the characterization of the population of the selected articles the extracted data is summarized in Table 2.

The principal sites of infection were urinary tract,[30,32,36] respiratory system,[30,32] bone joint,[30,33,34] orthopedic device-related infections,[33-35] digestive tract,[30,32] integumentary system,[32] cardiovascular system,[32] chronic osteomyelitis[35] and other non-specified infection sites.[30,32] In some cases, the development of uncomplicated sepsis,[32] severe sepsis,[30,32] and septic shock.[32] The course of infection was specified to be principally acute[33] and chronic.[34] The infection was mentioned to be acquired from the community.[32] The main etiological agents were *E coli*,[31,32,35,36] *Staphylococcus aureus*,[33-35] K. pneumonia,[31,36] methicillin-resistant coagulase-negative staphylococci,[34] *Streptococcus* spp.[32] and other polymicrobial infections.[33]

The use of antibiotic therapy through the subcutaneous route was studied with the following indications; difficult venous access,[30,32,36] contraindication for the oral route,[30,31,36] contraindication for IM injection,[30,31] difficulty maintaining the venous access,[30,32] facilitate hospital discharge or avoid hospitalization,[30,36] palliative care decision,[30,31] pathogen's resistance profile,[35] polymicrobial infection, history of drug-related adverse events, risks related to venous access[32] or absence of active oral antibiotic drug.[30]

Characterization of the Treatment

The antibiotics used were Ceftriaxone,[30,32,35] Ertapenem,[21,30,31,35] Teicoplanin,[30,33,34] Amikacin,[31] Ceftazidime[35] and other non-specified antimicrobials.[30] The dose for Ceftriaxone in the study conducted by Roubaud-Baudron et al was 1g SC in 91.9% of the patients,[30] for Gauthier et al it was 1.046 mg/day SC in 97.3% of the cases[32] and for Pouderoux et al[35] a dose of 1 g/day SC. For Teicoplanin in the study by Peeters et al, there was a loading dose (85.9% of the cases) of 5 injections of 5.7 mg/kg/12 h SC followed by a median dose of 5.7 mg/kg/day SC[33] and in the El Samad et al[34] review a loading dose of 5 injections of 12 mg/kg/12 h SC and a maintenance dose of 5.7 mg/kg/day SC adjusted to renal function. In the case of Ertapenem, Forestier et al used a dose of 1 g/day SC (500 mg in chronic renal failure) and for Pouderoux et al 1 g/12 h or 1 g/day SC (in patients with chronic renal failure). The use of Ceftazidime following Pouderoux et al[35] was 2 g/day SC (adjusted to renal failure).

A comparison between the use of antibiotic therapy by intravenous (IV) or subcutaneous routes of administration was carried out by Gauthier et al, Peeters et al, and Forestier et al[32,33,36] In the study led by Forestier et al, for 20% of the patients with subcutaneous administration, the antimicrobial was previously administered intravenously for a mean time of 5 days[36] as well as in the study by Roubaud-Baudron et al,[30] the SC route was used after the start of antibiotic therapy through IV or oral route in 48.8% of cases. Moreover, in the study by Pouderoux et al,[35] one patient received 8 days of ceftriaxone before receiving ertapenem. In some studies, there was a companion drug in the antibiotic therapy, such as Fluoroquinolones,[33] Rifampicin,[33,34] Streptogramin,[33] Oxazolidinones, Lincosamides, Fusidic acid, Penicillins,[34] and Aminoglycoside.

The report of the duration of the antibiotic treatment between the different studies was heterogeneous, being a common factor in calculating the mean days of treatment without presenting other statistics to determine the standard deviation. The mean days of treatment were 21 days,[30-36] considering that the study by Pouderoux et al[35] was an outlier, as they had a particularly longer follow-up period of 433 days. The application is described to be within the hospital,[20,32,36] homes, nursing homes, acute geriatric units, rehabilitation centers, and long-term care facilities.[30,31,34,35]

The preparation of the administered solution was specified in some of the studies as well as the equipment used and the time of application. The generally preferred diluent was normal saline solution .9%[30,31,33,35] followed by glucose solution 5%[30,31] and water.[30] The main equipment used were butterfly needles,[30,33,35] subcutaneous catheters,[30,31] and non-rigid catheters.[30] Regarding the time of application, 4 articles report a time greater than 30 minutes,[33,35] 2 less than 30 min[30,31] and another didn't refer to it.[32] Moreover, the site of application fluctuated between the thigh,[30,31,35] flank,[30,36] abdominal wall,[31] scapular zone,[31] and other non-specified locations.[30]

A diverse range of paraclinical tests was used in the studies for different purposes as; plasmatic levels of the antibiotic (Cmin),[33-35] bacteriological sample,[35,36] acute phase reactants, leukocytes, protein C reactive,[31] serum assays,[34] albumin level[32] and mean estimated creatinine clearance by MDRD formula rate.[36] The characterization of the treatment is specified in Table 3.

Characterization of the Outcome

The outcome was classified as success, failure, withdrawal, and mortality. The success was defined as clinical resolution, improvement, or remission of the infection; meaning lack of symptoms or signs of infection associated with the absence of relapse after the end of the antibiotic treatment.[34] The failure referred to persisting infection with adequate antimicrobial management, relapse after the suspension of the antibiotic, requirement of iterative surgical procedure, superinfections and/or fatal outcome, also including the need for change of therapeutic approach.[33-35] The details of the characterization of the outcome of the studied articles is summarized in Table 4.

Peeters et al, and El Samad et al[34,33] investigated the use of subcutaneous teicoplanin in osteomuscular infection caused by s. There was sepsis-related death in 2% of the sample.[33] On the other hand, they reported 7 adverse events consisting in 5 cutaneous rashes, 1 episode of headache, and pancytopenia with no difference between intravenous or subcutaneous route.

Peeters et al studied the safety and pharmacokinetics of intravenous or subcutaneous teicoplanin. They reported a

Table 3. Treatment Characteristics of Included Studies.

	Antibiotic Therapy				
Author (s)	Antibiotic	Duration of the Subcutaneous Antibiotic Therapy (Mean days)	Preparation of the Antibiotic	Time of Application (minutes)	Context of Administration
Pouderoux et al	Ertapenem (70%) Ceftriaxone (20%) Ceftazidime (10%)	433	Diluted in 50 mL of .9% NaCl	30-45	Home (70%) Nursing home (30%)
Forestier et al	Ertapenem (100%)	10	Diluted in 50 mL of .9% NaCl	30	Hospitalized (8%) Outpatients (92%)
El Samad et al	Teicoplanin (100%)	42	Diluted in 50 mL of .9% NaCl	30	Hospitalized (100%)
Peeters et al	Teicoplanin (100%)	43	Diluted in 50 mL of .9% NaCl	30-60	Hospitalized (100%)
Gauthier et al	Ceftriaxone (100%)	8	Not reported	Not reported	Hospitalized (100%)
Roubaud-Baudron et al	Ceftriaxone (74%) Ertapenem (14%) Teicoplanin (5%) Others (7%)	16	NaCl 0.9% (64%) GS5% (14%) Water (11%) Other (11%)	Rapid (<5) (38%) Slow (>5) (61%)	Acute geriatric (41%) Internal medicine department (23%) Rehabilitation centres (17%) Long term care facilities (19%)
Noriega et al	Ceftriaxone (64%) Ertapenem (26%) Amikacin (10%)	6	Diluted in 50-100 mL of .9% NaCl (80%) or 5% GS (20%)	15-30 min	Acute geriatric unit (100%)

NaCl: Sodium Chloride solution; GS: Glucose solution.

clinical resolution of 60%; probably secondary to significant selection bias because the patients were exclusively from a center dedicated to managing complex bone joint infection with a high-risk of failure.[33] Additionally, treatment failure was recorded in 45%, including persistent infections (67%), relapses (22%) and/or superinfections (48%), leading to iterative surgical procedures in 35% of the cases, including 2 limb amputations. There was sepsis-related death in 2% of the sample.[33] On the other hand, they reported 7 adverse events consisting in 5 cutaneous rashes, 1 episode of headache, and pancytopenia with no difference between intravenous or subcutaneous route.

El Samad et al[34] analyzed the subcutaneous teicoplanin's tolerability and plasma levels of mentioned a clinical improvement in 72% of the cases, remission in 12%, failure in 16%, withdrawal for side effects in 10% (secondary to neutropenia and deterioration of renal function) and no deaths. They evaluated the adverse reaction at second, 14, 28 and 42 day finding local reaction, pain, swelling, erythema, and other with a mayor prevalence in days 14 and 28. The main systemic reaction were deterioration of chronic renal failure and vascular disease (3 patients).

The study by Pouderoux et alalso investigated subcutaneous antibiotic therapy for osteomuscular infections but using ceftazidime, ceftriaxone and ertapenem in prolonged suppressive therapy. Reported a clinical resolution/improvement in 60% of the patients, failure was considered in 10% secondary to a relapse under ertapenem therapy and the treatment was switched from subcutaneous to intravenous route in 10% of the sample due to the development of terminal renal failure unrelated to treatment with the requirement of hemodialysis.[35] The therapy was withdrawn in 30% of the cases for side effects (skin necrosis, non-controlled epilepsy and hypereosinophilia) and 10% died of rectal cancer.[35]

Forestier et al studied subcutaneous ertapenem as treatment for urinary infections caused by BLEE stablished a clinical resolution of 100% at the end of the treatment and 3 months later, 56% of the patients persisted without a new infection. There was a relapse of 20% of the patients and 24% presented

Table 4. Outcome Characteristics of Included Studies.

	Complications		Outcome			
Author (s)	Local	Systemic	Success	Failure/Change of Therapeutic Approach	Withdrawal	Mortality
Pouderoux et al	Orange-peel skin aspect Transient injection-site pruritus Cutaneous necrosis	Cholestatic hepatitis (10%) Hypereosinophilia (20%) Imbalanced epilepsy (10%)	Clinical resolution/ improvement 60%	Failure (10%) SC injections were switched to an IV route (10%) Developed terminal kidney failure unrelated to treatment	Withdrawn for side effects (30%) Skin necrosis Non-controlled epilepsy, cutaneous rash and pruritus Hypereosinophilia	Died of rectal cancer (10%)
Forestier et al	Localized skin necrosis (4%)	-	Clinical resolution/improvement at the end of the treatment (100%) 3 months after the end of treatment (56%) without a new UI.	Relapse (20%) UI linked to another bacteria (24%)	Not reported	Not reported
El Samad et al	Pain (43%) Swelling: <5 cm (60%) >5 cm (33%) Erythema: <5 cm (57%) >5 cm (29%) Warmth (35%) Itching (25%) Hematoma (8%) Telangiectasia (<1%)	Neutropenia (7%) Deterioration of renal function (10%)	Clinical resolution/improvement (72%) Remission (12%)	Failure (16%)	Withdrawn for side effects Neutropenia (7%) Chronic renal failure and vascular disease presented a slight deterioration of renal function (10%)	Not reported
Peeters et al	Cutaneous rashes (8%)	Headache (2%) Pancytopenia (2%)	Clinical resolution/improvement (60%)	Failure (45%) Persisting infections (67%) Relapse (22%) Superinfections (48%)	Not reported	Sepsis-related death (2%)
Gauthier et al	-	-	Clinical resolution/improvement (76%)	Failure (3%) Change of therapeutic approach to oral intake (5%)	Adaptation to the antibiogram (1%)	Mortality rate (18%)
Roubaud-Baudron et al	Pain (13%) Induration (8%) Haematoma (7%) Erythema (3%)	Hypereosinophilia Diarrhea Acute renal failure Cholestasis Confusion	Clinical resolution/improvement (89%)	Failure (5.5%) Change of therapeutic approach to another administration route (11%)	Not reported	Mortality rate (5.5%)
Noriega et al	Edema at the infusion site Erythema at the infusion site	Not reported	Clinical resolution/improvement (82%)	Change of therapeutic approach to IV (3%)	Not reported	Mortality rate (15%)

SC: Subcutaneous; IV: Intravenous; UI: Urinary Infection.

infections related to different bacteria. There were no withdrawals or deaths during the study period. The only local complications was skin necrosis (4%)[36]

The others studies analyzed subcutaneous therapy of infections of different origin in elderly patients. Gauthier et al analyzed ceftriaxone. The clinical resolution rate was of 76%, failure was described in 3%, change of therapeutic approach to oral intake was necessary in 5%, adaptation to the antibiogram in 1% and a mortality rate of 18%.[32] Roubaud-Baudron et al[30] recounted a clinical success in 89% of the patients, failure in 5.5%, change of therapeutic approach to another administration route in 11% and a mortality rate of 5.5%. And Noriega et al stated a clinical resolution of 82% of the cases, a change of therapeutic approach to IV was required in 3%, there was no need to withdraw and a mortality rate of 15%.[31]

The main local complications described by these authors were pain (13%), hematoma (7%) erythema (3%). The main systemic complications were hyper eosinophilia, diarrhea and acute renal failure only reported by Roubaud-Baudron et al[30]

In relation to factors associated with a positive outcome; the use of Lidocaine was described by Roubaud-Baudron et al, The clinical resolution rate was of 76%, failure was described in 3%, change of therapeutic approach to oral intake was necessary in 5%, adaptation to the antibiogram in 1% and a mortality rate of 18%.[32] Roubaud-Baudron et al[30] recounted a clinical success in 89% of the patients, failure in 5.5%, change of therapeutic approach to another administration route in 11% and a mortality rate of 5.5%. stated a clinical resolution of 82% of the cases, a change of therapeutic approach to IV was required in 3%, there was no need to withdraw and a mortality rate of 15%.[31]

To tend to decrease the occurrence of complications, but not significantly ($P = .097$).[30] Peeters et al[33] recounted that the return to baseline of protein c reactive value within the first month was associated with a lower risk of treatment failure (OR, .214; 95% CI, .051-.852).

In the contrary, there were also factors associated with a negative outcome, as were the correlation with the class of administered antibiotic, in this case Teicoplanin, the rapid antibiotic infusion (<5 min) and the use of a rigid catheter, mentioned in the review by Roubaud-Baudron et al[30] Noriega et al described that despite the low proportion of complications observed and their low clinical relevance, their presentation had a direct correlation with the administration of Amikacin and the use of glucose solution.[31] Peeters et al[33] found that high Teicoplanin Cmin (>1.5 mg/L) had a correlation with unfavorable outcome and higher mortality rate. There was an independent association between the presence of pertinent variables associated with therapeutic failure with a P-value <.15 were inflammatory systemic disease (OR, 5.600; 95% CI, 1.056-29.683), diabetes mellitus (OR, 5.143; 95% CI, .951-27.826), and in situ abscess (OR, 4.073; 95% CI, 1.420-11.684).

Discussion

This study shows that the use of subcutaneous antibiotic therapy in elderly palliative patients can be a safe and effective alternative for certain infections. Nevertheless, to half of the patients may present local reactions that, although may not be serious, can impair the patient's quality of life. The studies included in this review have a great degree of heterogeneity given their different designs, types of infections, types of antibiotics, time of follow-up, assessment of antimicrobial effectiveness, scales employed to measure outcomes, and outcomes.[30-36] For this reason, it is crucial to analyze the data of patients at end of life. Which makes the choice of subcutaneous antibiotic therapy to be made with caution, use it independently in each scenario, and choose subcutaneous antibiotic therapy with caution based on the patient'spatients' needs and clinical condition.

In palliative care, assessing antibiotic effectiveness has additional challenges, as the objective of the treatment has to be individualized and balanced between treating infection and alleviating the associated symptom burden.[14,37-39] Additionally, palliative care clinicians need to consider the objective of the treatment by analyzing the clinical scenario and considering the patient and family perspectives.[40] To this aim, advanced care planning and shared end-of-life decisions are paramount tools to offer quality palliative care.[40] Also, standardized and validated scales to assess symptom control aid the clinicians' daily practice.[28,39,41] The elderly population is characterized by having multiple comorbidities, metabolism alterations, a high rate of polypharmacy, diminish functionality, frailty, and the inability to receive intravenous or oral medications.[42] Exposing elderly patients with advanced chronic illnesses to antimicrobial treatments conveys risks (ie, adverse events or drug interactions) that may lead to a series of complications that could be lethal.[27,38] All of these factors make elderly palliative care patients a special population vulnerable and with special management needs.[42–44]

Due to the given review findings, we think the correct use of subcutaneous antibiotics in elderly palliative care patients should be performed under the following circumstances. First, when the patients can be taken care of by a multidisciplinary team where there is a palliative care physician and an infectious disease specialist. Second, when the elderly palliative care patient wants to remain at home and there is no other route to administer the antibiotics. Third, when the risks related to the subcutaneous route are reasonable and accepted by the patient. Fourth, when the bacteria causing the infection characteristics are suitable to be treated with one of the antibiotics that can be given through the subcutaneous route. Fifth, when the infection in place is contained and has not evolved into sepsis. Sixth, when the infection compromises one of the sites reported on the studies here-in summarized. Seventh, when the patient doesn't have more than one infection and its origin is clearly identified. Eight, when the patient counts with a good career support that is

knowledgeable of the subcutaneous route usage. Nineth, when the patient is not at the end of life. Tenth, the patient can be followed in time by a domiciliary team that can monitor the infection resolution or treat the side effects of the antibiotic SC therapy.[45] If this ten conditions are fulfilled, the caring process of using antibiotic subcutaneous therapy may be safe, feasible and useful for the patient while remaining comfortable at home.

Limitations of the Study

The review has limitations to be considered. The search was conducted in the English language using only 2 databases and excluded grey literature, so there is a chance relevant articles might have been missed. Moreover, our results should be considered hypothesis-generating, given the low methodological quality and heterogeneity of the studies reviewed. Also, SC antibiotic therapy cost-effectiveness was not assessed in this review nor any of the retrieved studies. For insurance stakeholders, this unexplored factor is crucial for the development and integration of this type of practice. Another limitation is the lack of patients' reported outcomes, which couldn´t be reported in the review because they were not considered in the included studies. Finally, we did not include ongoing or unpublished studies uploaded on clinicaltrials.gov that might be relevant to our review.

Conclusions

The best route of antibiotics administration for the treatment of infections continues to be a research area in palliative care patients. Here in, we describe their effectiveness and safety through the subcutaneous route in elderly patients. From our review, pilot studies have found a limited number of antibiotics that can be safely used to treat specific infections. Nevertheless, the data isn´t robust enough to recommend their use, except for selected patients.

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Author Contributions

MASC, LMVE, JEC, LVG, MMA, MXL made a substantial contribution to the concept or design of the work, or acquisition, analysis, or interpretation of data, CMO, and JAL, made substantial contributions to data analysis.

Declaration of Conflicting Interests

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Ethical Considerations

Given the nature of the study, it did not require ethical endorsement; however, the citation standards corresponding to copyright were considered and all authors are responsible for the accuracy and originality of the full text.

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