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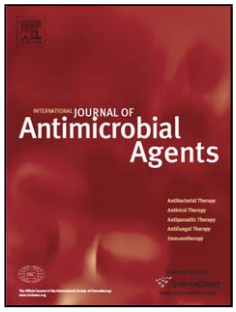

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Patients included in randomised controlled trials do not represent those seen in clinical practice: focus on antimicrobial agents

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ABSTRACT

Clinicians rely on the findings of randomised controlled trials (RCTs) to formulate clinical decisions regarding individual patients. We examined whether patients included in RCTs focusing on antimicrobial agents are representative of those encountered in real-life clinical situations. PubMed was searched for RCTs referring to the field of infectious diseases. Data regarding the exclusion criteria of the identified RCTs were extracted and critically evaluated. In total, 30 trials (17 referring to respiratory tract, 5 to skin and soft-tissue, 4 to intra-abdominal, 2 to gynaecological and 2 to bloodstream infections) were included in the study. All retrieved RCTs reported extensive exclusion criteria. After comparing in a qualitative manner (based on our clinical experience) the eligible patient population in the identified RCTs with the respective population that would be encountered in general practice, it was observed that the abovementioned patient populations differ considerably. In conclusion, RCTs in the field of infectious diseases use extensive and stringent exclusion criteria, a fact that may lead to considerable difference between the patient populations of RCTs and those viewed in clinical practice. The application of the findings of RCTs to the care of individual patients should be performed cautiously.

1. Introduction

Clinicians are confronted with a wide variety of clinical questions and make decisions that affect individual patients. In this clinical decision-making process, evidence-based medicine may play a significant role by collecting and evaluating the best available evidence. Randomised controlled trials (RCTs), and meta-analyses of RCTs, are considered to provide evidence of the highest grade [1,2]; thus, their findings, which are often easily accessed [3,4], are implemented to answer clinically relevant questions [5].

The study populations of RCTs consist of individuals who must meet specific criteria, predefined by the researchers. In an attempt to increase homogeneity of the study population, researchers tend to use strict inclusion criteria. Thus, a proportion of screened patients do not fulfil the criteria for entry into RCTs; often this proportion of excluded patients seems not to be negligible. For instance, in a recent RCT evaluating the usefulness of silver-coated endotracheal tubes in preventing ventilator-associated pneumonia, 84% of the initially screened patients were excluded from the primary efficacy analysis [6]. In addition, the use of strict inclusion criteria may also contribute to the explanation of several paradoxical findings of RCTs. For example, in a meta-analysis conducted by our research team [7], all included RCTs evaluating the short versus long antimicrobial treatment of children with acute bacterial meningitis reported no death due to this well known fatal infection (namely bacterial meningitis), a fact that presumably raise concerns regarding the external validity of the above RCTs [7].

Taking all the above into consideration, this study was performed to examine, by reviewing the exclusion criteria of RCTs, whether the patients included in RCTs are representative of those seeking medical care in real-life clinical situations.

2. Data sources

Potentially eligible articles were identified through search of the PubMed database. An article was considered eligible for inclusion in this study if it was a RCT that enrolled individuals with infections. Inclusion and exclusion criteria used in each RCT should have been clearly stated in the text. The first 30 articles that met all the above criteria and for which a full-text was obtained were included in this study. No lower time limit was applied to the search.

3. Data extraction and evaluation

The following information was extracted from each of the included RCTs: first author and year of publication; type of infection; characteristics of the groups to which the included patients were assigned; and inclusion and exclusion criteria as presented in the text by the authors of each study. Based on our clinical experience, the patient population that would be regarded as eligible for inclusion in each RCT was compared, in a qualitative manner, with the patient population with the same infection that would seek medical care in general practice.

Thirty RCTs were included in this study [8–37]. Their characteristics are summarised in Table 1. Seventeen (56.7%) of the RCTs referred to respiratory tract infections [8,10,12,15,16,19,21,24–26,28,29,31,32,35–37], five (16.7%) to skin and soft-tissue infections [9,11,14,22,27], four (13.3%) to intra-abdominal infections [17,23,30,33], two (6.7%) to gynaecological infections [18,34] and two (6.7%) to bloodstream infections [13,20].

The exclusion criteria reported in each of the 30 RCTs [8–37] included in this study were extensive (Table 1). After comparing, in a qualitative manner, the patient population included in each RCT with the patient population with the same infection that would be viewed in general practice, it was found that the abovementioned patient populations appear to differ substantially.

4. Discussion

The main finding of this study is that the incorporation of extensive and stringent exclusion criteria of RCTs may lead to the enrolment of patients who are considerably different from those encountered in clinical practice. Thus, the conclusions generated from RCTs may not apply to a considerable proportion of patients viewed in real-life clinical situations.

Although RCTs and meta-analyses are considered to represent the top in the hierarchy of evidence-based medicine [38], the applicability of their findings in general practice has been questioned [39–41]. For example, it has been

supported that RCTs may fail to reveal adverse events associated with the use of several drugs, such as the arrhythmias related to the administration of quinolones [42]. As a result, such drugs had received approval from the regulatory agents, on the basis of findings of RCTs, and were then withdrawn from the market [43]. It seems that post-marketing (observational) studies may be more reliable than RCTs in evaluating the safety of drugs [44,45]. The failure of RCTs to address safety issues of medications adequately may be due to the fact that adverse events are often under-reported in RCTs or because the patients included in RCTs are less likely to experience adverse events compared with patients encountered in real life.

The exclusion criteria are clearly stated in the majority of RCTs by their authors, leaving the responsibility to clinicians to decide whether or not to apply their findings to individual patients. However, one may consider that, at least, a proportion of clinicians may not pay sufficient attention to the exclusion criteria of published trials owing to time constraints. Besides, clinicians, although aware of the exclusion criteria used in each trial, may tend to overlook them when it comes to decision-making; for example, they may choose to use an effective drug overlooking the fact that it has not been tested in specific group of patients, such as elderly individuals.

Exclusion from trials of several patients, such as those with known hypersensitivity to the study drugs, appears obligatory from an ethical point of view. One might add that this should be also the case for pregnant women,

elderly patients, immunocompromised patients or those with renal or hepatic insufficiency. However, given that the prevalence of, for example, renal insufficiency [46–48] or elevated liver enzymes levels [49] in the outpatient setting is considerable, such stringent exclusion criteria may lead to the exclusion of many patients encountered in real life. Indeed, there is evidence that specific vulnerable populations (such as the abovementioned) have been under-represented in RCTs [50–53], a fact that presumably threatens their external validity.

To cope with this issue (namely the under-representation in trials of the abovementioned vulnerable populations), several approaches could be considered. First, one may suggest matching the population to be included in the RCT to the respective population that is expected to be encountered in general practice, i.e. quota-sampling techniques may be incorporated to ensure the enrolment of specific segmented subgroups of populations [54]. Notably, the US Food and Drug Administration (FDA) has approved quota-sampling techniques for the enrolment of Black individuals in RCTs. Such a strategy could also be adopted for other vulnerable patients such as pregnant women or elderly and immunocompromised patients. In this case, frequently conducted interim analyses may attenuate, at least to some degree, the risk of enrolment of vulnerable populations in RCTs. Second, concurrent conduction of two different RCTs, one enrolling low-risk and another enrolling high-risk patients, may also be an alternative approach. Finally, surveillance data collected by the pharmaceutical industry, the regulatory agents, researchers and clinicians

regarding experience of the usage of newly licensed drugs in high-risk populations may also be very useful in clarifying safety issues [55–57].

The current study has limitations that should be taken into consideration. First, we deliberately chose to review a number of trials as high as 30 and we selected to include only those referring to the field of infectious diseases. However, it may be anticipated that our findings would not be substantially different even if we considered a greater number of trials or trials referring to medical fields other than infectious diseases. In addition, since it was not feasible to quantify the proportion of real patients who would meet the exclusion criteria set in each of the evaluated RCTs, this issue has been assessed only in a qualitative manner. However, every experienced clinician, by reviewing Table 1, could easily note that a great proportion of patients he/she takes care for indeed meet the exclusion criteria of RCTs.

5. Conclusions

Patients included in RCTs appear to differ substantially from those seen in clinical practice. This fact may limit the applicability of the evidence derived from RCTs to real life. Thus, given that evidence-based medicine remains a useful tool in the decision process, clinicians should consider the limitations of the patient population involved in each clinical trial they are referring to in order to make treatment decisions as applied to individual patients encountered in every-day clinical practice.

6. Main messages

6.1. What is already known on this topic?

1. Clinicians rely on the findings of RCTs to formulate clinical decisions regarding individual patients.
2. In an attempt to increase homogeneity of study population, researchers tend to use strict inclusion criteria.

6.2. What this study adds?

Incorporation of extensive and strict exclusion criteria of RCTs may lead to enrolment of patients that are considerably different from those seen in clinical practice.

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Competing interest

None declared.

Ethical approval

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Table 1

Characteristics of randomised controlled trials included in the present study

First author, year	Type of infection	Compared groups (Group A) vs. (Group B) vs. (Group N)	Inclusion criteria	Exclusion criteria
Conde, 2009 [8]	TB	All patients received isoniazid, rifampicin and pyrazinamide at standard doses; (moxifloxacin + placebo) vs. (ethambutol + placebo)	Patients ≥18 years with clinical signs and symptoms of pulmonary TB, including an abnormal chest radiograph and at least one sputum smear with acid-fast bacilli visible by Ziehl–Neelsen staining	Haemoglobin concentration <70 g/L; AST/ALT concentration >3× ULN; creatinine concentration >2× ULN; electrocardiogram with a QTc interval >450 ms; pregnancy/breastfeeding; silicotuberculosis; history of severe adverse reactions to fluoroquinolones or other study agent; seropositivity for HIV with $CD4^+$ cell count <200 cells/μL; baseline culture did not grow *Mycobacterium tuberculosis* or grew a strain of *M. tuberculosis* that was resistant to isoniazid, rifampicin or ethambutol
Dworkin, 2009 [9]	Herpes zoster	(Controlled-release oxycodone + famciclovir) vs. (gabapentin + famciclovir) vs. (placebo + famciclovir)	Patients ≥50 years with herpes zoster within 6 calendar days of rash onset; worst pain in the past 24 h ≥3 on a 0–10 NRS [a]; ability to provide written informed consent	Major: prodrome of unilateral dermatomal pain in the area of the rash beginning >7 days prior to rash onset; cutaneous or visceral dissemination; immunosuppression that in the investigator's opinion would significantly

		increase the risk of dissemination; any clinically significant medical condition, laboratory abnormality or cognitive impairment; systemic antiviral therapy within 8 weeks prior to baseline, except for treatment with aciclovir, famciclovir or valaciclovir for herpes zoster if the subject agreed to take study famciclovir instead; alcohol or drug abuse history within the previous 5 years; use of tricyclic antidepressants, antiepileptic medications, mexiletine, any topical analgesics or nerve block of the affected or adjacent dermatomes within 2 weeks prior to the baseline visit and for 1 month after randomisation; use of opioid analgesics or tramadol on a regular basis within 2 weeks prior to the baseline visit and for 1 month after randomisation (use of these medications for prodromal or herpes zoster acute pain before the baseline visit was allowed if the patient was willing to discontinue the medication to enrol); unwillingness or inability to limit use of

				acetaminophen to a maximum of 2500 mg/day while receiving third-tier rescue medication (see below); history of herpes zoster prior to the current episode. Minor: Women could not be lactating and had to be surgically sterile or postmenopausal for 2 years, or with a negative urine pregnancy test and using a medically acceptable contraceptive regimen for at least 60 days prior to the baseline visit and agreeing to continue such use until 30 days after the final dose of study medication
Ermers, 2009 [10]	RSV infection	[Extra fine hydrofluoroalkane-beclomethasone diproprionate] vs. (placebo)	Infants <13 months admitted to hospital for LRTI with a positive immunofluorescence result for RSV infection in epithelial cells from nasopharyngeal aspirates	Infants with: (a) previous steroid treatment; (b) history of cardiac or pulmonary disease; and (c) previous illness with wheeze
Euba, 2009 [11]	Chronic staphylococcal osteomyelitis	(6-week parenteral + 2-week p.o. cloxacillin treatment) vs. (8-week p.o. rifampicin + co-trimoxazole combination treatment)	Patients who had undergone surgery for chronic non-axial osteomyelitis due to *Staphylococcus aureus*, with or without associated foreign bodies (1991–1996). Diagnostic	Patients with prosthetic joint infections, polymicrobial infections, or infections with cloxacillin-, co-trimoxazole or rifampicin-resistant isolates

			criteria included inflammatory signs and/or sinus drainage for ≥10 days, compatible radiography results and the presence of necrotic bone	
Plint, 2009 [12]	Bronchiolitis	(Nebulised epinephrine + p.o. dexamethasone) vs. (nebulised epinephrine + placebo) vs. (nebulised placebo + p.o. dexamethasone)	Infants 6 weeks–12 months with bronchiolitis who were seen at participating emergency departments with a score of 4–15 on the RDAI	Infants who received: (a) bronchodilator treatment before assessment; and (b) oral/inhaled corticosteroids during the preceding 2 weeks. Infants with: a previous episode of wheezing/a diagnosis of asthma/previous bronchodilator use/any chronic cardiopulmonary disease/immunodeficiency/infants in severe distress (defined as a pulse rate >200 beats/min, a respiratory rate >80 breaths/min or an RDAI score >15) or with profound lethargy. Infants who had been exposed to varicella within the preceding 3 weeks. Infants born <37 weeks of gestation who had a corrected age of <6 weeks at presentation. Insurmountable barriers to communication

				with the family (a language barrier or lack of a telephone on the part of the parent or guardian)
Rehm, 2009 [13]	*S. aureus* bacteraemia with or without infective endocarditis	(Daptomycin) vs. [standard therapy (semisynthetic penicillin or vancomycin, each with initial low-dose gentamicin)]	Patients ≥18 years with at least one blood culture growing *S. aureus* within 2 days before first administration of the study drug	CL_{Cr} < 30 mL/min and the presence of known osteomyelitis, polymicrobial bacteraemia or pneumonia
Pertel, 2009 [14]	Cellulitis and erysipelas	(Daptomycin for 7–14 days) vs. (vancomycin for 7–14 days)	Patients ≥18 years with a primary diagnosis of cellulitis or erysipelas requiring hospitalisation and i.v. antibiotic therapy Onset of symptoms and signs must have occurred within 3 days of the first dose of study medication, and a temperature >37.5 °C orally or >38.0 °C rectally had to be recorded within 48 h before enrolment. The infection had to be at an anatomical location that allowed for clear assessment of the erythema marginatum	Patients were excluded from the study if they: (a) required emergent surgical intervention; or (b) if surgery constituted curative treatment, or if the cellulitis was associated with a wound or ulcer that required incision, drainage or debridement. Other excluding conditions included: perirectal abscess; hidradenitis suppurativa; third-degree burn infections; buccal, facial, periorbital or perianal cellulitis; known or suspected osteomyelitis or bacteraemia; ANC ≤ 500 cells/mm^3; CL_{Cr} < 30 mL/min; rhabdomyolysis; known allergy or intolerance to study medications; required systemic corticosteroids or antibiotics other than the study drugs or

				systemic antimicrobial therapy for >24 h during the 72 h before the first dose of the study drug, unless they had been on the antimicrobial for ≥72 h without clinical improvement; pregnant or lactating women
Pareek, 2008 [15]	LRTIs	(Cefuroxime/sulbactam for 7–10 days) vs. (amoxicillin/clavulanic acid for 7–10 days)	Patients 18–65 years with moderate to severe LRTIs such as CAP or AECB of sufficient severity to require parenteral therapy and hospitalisation Diagnosis of LRTI was confirmed by chest X-ray showing localised infiltrates and sputum smear examination showing <10 epithelial cells and >25 leukocytes or pus cells per low power field (×100), together with any three of the following symptoms: fever ≥37.5 °C, productive cough, production of purulent sputum, dyspnoea and chest pain along with the presence of at least two of the following signs: WBC count ≥10	Hypersensitivity or allergy to cephalosporins, penicillins, sulbactam, clavulanic acid or any other constituents of the study medications. Patients with a clinical history suggesting infections due to resistant organisms, patients with CF or fungal infection, patients clinically suspected of suffering from viral infections, neutropenia, lung cancer, severe bronchiectasis, active TB or patients seropositive for HIV or any other progressive fatal disease. Patients with abnormal renal function (serum creatinine ≥1.5 mg/dL for males and ≥1.4 mg/dL for females), abnormal hepatic function (AST and ALT, total bilirubin or alkaline phosphatase >2.5× ULN), left ventricular dysfunction or cardiac arrhythmia.

			× 10^9/L, bronchial breathing sounds, decreased air entry, rhonchi or crepitations	Pregnant or lactating women and women of childbearing potential not practicing contraception were not considered to be eligible for entry into the study
Desrosiers, 2008 [16]	ABS	(Telithromycin p.o. 800 mg qd for 5 days) vs. (amoxicillin/clavulanic acid p.o. 875/125 mg b.i.d. for 10 days)	Male or non-pregnant female outpatients ≥18 years with a clinical diagnosis of ABS based on the following criteria: signs and symptoms lasting >7 days and <28 days; purulent anterior or posterior nasal discharge; one additional major sign and symptom (facial pain/pressure/tightness over the maxillary sinuses; nasal congestion/obstruction; hyposmia/anosmia; fever defined by a temperature of >38 °C (oral)/>38.5 °C (tympanic)/>39°C (rectal) or two minor signs and symptoms (headache, halitosis, dental pain, ear pressure/fullness,	Patients with 43 episodes of sinusitis requiring antibiotics in the previous 12 months or those with chronic sinusitis (signs and symptoms lasting >28 days) were excluded from the study, as were patients who had received antibiotic treatment (>24 h duration) in the 30 days prior to enrolment. Other exclusion criteria: surgery in the last 6 months; sinus puncture or lavage in the previous 7 days; long-term (≥4 week) use of nasal decongestants; and intranasal corticosteroid/short-term systemic corticosteroid therapy within 10 days prior to enrolment

			cough, fatigue). Patients also had to have abnormal maxillary sinus X-rays or limited sinus CT scans or sinus ultrasound in the 48 h prior to inclusion, defined by the presence of at least one of the following: air/fluid level; total opacification; mucosal thickening ≥10 mm. Patients' written informed consent was required prior to enrolment	
Lucasti, 2008 [17]	cIAIs (Phase III study)	(Doripenem 500 mg q8h as a 100 mL i.v. infusion over 1 h) vs. (meropenem 1 g q8h as a 20 mL i.v. bolus injection over 3–5 min)	Patients ≥18 years were eligible if they had clinical evidence of cIAI, underwent surgical intervention within 24 h of study entry and required antibacterial therapy in addition to surgical intervention. Eligible cIAI diagnoses included cholecystitis with rupture, perforation or progression of the infection beyond the gallbladder wall; diverticular disease with	Patients with uncomplicated IAI (e.g. bowel disease without perforation), abdominal wall abscess or intra-abdominal processes unlikely to have an infectious aetiology or to be managed by staged abdominal repair or an open abdomen technique were excluded. Other exclusion criteria were: infected necrotizing pancreatitis; pancreatic abscess; APACHE II score >30; rapidly progressive or immediately life-threatening illness (e.g. acute hepatic failure,

		perforation or abscess; appendiceal perforation or periappendiceal abscess; acute gastric and duodenal perforations [only if operated on at >24 h after the perforation had occurred (in patients operated on at <24 h, a full course of antibiotic treatment is not necessary)]; traumatic intestinal perforation (only if operated on at >12 h); peritonitis due to perforated viscus, occurring postoperatively or due to other focus of infection; and/or intra-abdominal abscess, including in the liver or spleen. Patients with a postoperative infection and those failing a prior antibacterial regimen were eligible if they required further surgical intervention and ≥1 pathogens were isolated from the baseline culture of the intra-	respiratory failure, septic shock); unlikely survival to the end of the 6- to 8-week study period (i.e. moribund patients whom the investigator considered likely to die without completing the study despite antibiotic treatment); infection with a pathogen known to be resistant to the study drugs; need for concomitant antimicrobial agents other than vancomycin or amikacin; severe renal impairment (CL_{Cr} <10 mL/min); presence of hepatic disease (AST and ALT >4× ULN, haematocrit <25%, haemoglobin <8 g/dL); ANC < 1000 cells/μL (but neutrophil count to 500 cells/μL allowed if caused by the acute infection); platelet count <75 000 cells/μL (but platelet count to 50 000 cells/μL allowed if historically stable); immunodeficiency or use of immunosuppressive therapy; recent (≤30 days) participation in a study of an investigational drug or device; or systemic antibiotic therapy for cIAI lasting ≥24 h within the 48-h period before the first dose

			abdominal site of infection. In addition, ≥1 of the pathogens isolated had to be susceptible to both study drugs	of study drug. Patients with a history of hypersensitivity reactions to carbapenems, penicillins, other β-lactam antibiotics or β-lactamase inhibitors were also excluded
Martinez, 2009 [18]	Vulvovaginal candidiasis	(Single dose of fluconazole 150 mg + 2 oral capsules of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14) vs. (single dose of fluconazole 150 mg + placebo) for 28 days	Patients suffering from vaginal discharge associated with any of the following symptoms: itching and burning vaginal feeling, dyspareunia and dysuria, whose vaginal samples were positive for *Candida* spp. by culture method	Pregnancy, HIV-positive patients and those who were also positive for bacterial vaginosis or trichomoniasis; use of systemic or intravaginal antibiotic or antifungal agents currently or within the past 2 weeks of the appointment; menses during samples collection; and allergic responses to fluconazole
Noel, 2008 [19]	Recurrent or persistent AOM	(Levofloxacin oral suspension 10 mg/kg b.i.d. for 10 days) vs. [amoxicillin/clavulanic acid (14:1 ratio) oral suspension containing 45 mg amoxicillin/kg b.i.d. for 10 days]	Outpatient children 6 months to ≥5 years who had recurrent and/or persistent AOM. Recurrent disease was defined as ≥3 episodes of AOM in the 6 months before enrolment or ≥4 episodes over the year before enrolment. Persistent disease was defined as evidence of AOM that was unchanged or worsened after ≥3 days of treatment with an	Children with persistent disease after receiving amoxicillin/clavulanic acid that provided ≥90 mg/kg/day of amoxicillin. Children with a tympanostomy tube in the affected ear, who required systemic antibacterials other than study drug or used corticosteroids chronically [prednisone (or equivalent) ≥2 mg/kg or ≥20 mg/day for ≥14 days]. Other exclusion criteria included: serious bacterial infection that may have interfered with assessment of clinical response;

			antimicrobial regimen used to treat AOM	history of previous hypersensitivity or serious adverse reaction against any quinolone or β-lactam antibiotic; history or presence of musculoskeletal signs or symptoms that in the opinion of the investigator may have confounded future safety evaluation of musculoskeletal complaints
Pappas, 2007 [20]	Candidaemia and other forms of invasive candidiasis	(i.v. micafungin 100 mg qd) vs. (i.v. micafungin 150 mg qd) vs. (i.v. caspofungin 70 mg on Day 1 and 50 mg thereafter qd)	Patients ≥18 years who had a diagnosis of candidaemia defined as at least one blood culture positive for *Candida* organisms, or a diagnosis of non-candidaemic invasive candidiasis defined as a *Candida*-positive culture of a specimen obtained from a normally sterile site ≤96 h before Day 1 or receipt of the first dose were eligible for enrolment. In addition, patients were required to have at least one of the following characteristics: fever (temperature ≥38 °C) or	Patients were not eligible for enrolment if they were pregnant or nursing, had hepatic disease with a Child–Pugh score >9, had a life expectancy of <5 days and/or had proven or suspected *Candida* endocarditis, osteomyelitis or meningitis. Additional exclusion criteria included the presence of any of the following characteristics: current receipt of a cyclosporine; receipt of an echinocandin <1 month before randomisation; or receipt of systemic antifungal therapy for the current infection for 148 h (the daily dose could not exceed 1 mg/kg for amphotericin B, 5 mg/kg for lipid amphotericin B, 800 mg for fluconazole, 400 mg for

			hypothermia (temperature <36 °C); hypotension (defined as a systolic blood pressure of <90 mmHg or a decrease of 130 mmHg from the measurement at baseline); local signs and symptoms of inflammation; and/or radiological findings that suggested invasive candidiasis. Antifungal prophylaxis with an azole or systemic amphotericin B was allowed prior to enrolment, independent of dose, duration and route of administration	itraconazole or 12 mg/kg for voriconazole)
Réa-Neto, 2008 [21]	Nosocomial pneumonia (NP)	(i.v. doripenem) vs. (i.v. piperacillin/tazobactam)	Patients ≥18 years with signs and symptoms of NP, including non-ventilated patients and those with early-onset VAP (<5 days of ventilation), hospitalised for ≥48 h or who had been discharged within the past 7 days after being hospitalised for ≥48 h. Residents of chronic care facilities	Patients were excluded if: (a) the NP was known (prior to the study) to be caused by pathogens resistant to either meropenem or piperacillin/tazobactam (other than MRSA); and (b) they required concomitant systemic antimicrobial therapy (other than vancomycin or amikacin) in addition to study drug or had received systemic antibiotic therapy for ≥24 h in the 72-h

		were also eligible if admitted to the hospital with pneumonia. Eligible patients had a new or progressive infiltrate on the chest radiograph; either fever, hypothermia or changes in peripheral WBC count attributable to infection (i.e. ≥10 000/mm^3, >15% immature forms regardless of WBC count or leukopenia); and if intubated, a CPIS ≥5 (where the maximum score was 11). Patients had either respiratory failure requiring mechanical ventilation or at least two of the following signs and symptoms: cough; new-onset production of purulent sputum or other respiratory secretions, or a change in the character of sputum; auscultatory findings of rales or evidence of pulmonary consolidation; dyspnoea,	period before randomisation to study drug (unless they failed prior therapy for NP or developed symptoms of pneumonia with a new pulmonary infiltrate while receiving the prior antibiotic regimen). Other exclusion criteria were: APACHE II scores <8 or >25; mechanical ventilation for ≥5 days; presence of known bronchial obstruction or history of post-obstructive pneumonia (other than COPD); cavitary lung disease, primary lung cancer or another malignancy with lung metastases; ARDS; CF; *Pneumocystis jiroveci* (*carinii*) pneumonia; *Legionella* infection; active TB; immunocompromising illness; need for dialysis; and any rapidly progressive disease or immediately life-threatening illness. Patients with significant liver function abnormalities, neutropenia or thrombocytopenia, history of moderate or severe hypersensitivity to β-lactam antibiotics or β-lactamase inhibitors. Treatment with >1 dose of piperacillin/tazobactam or a carbapenem

			tachypnoea or respiratory rate ≥30/min; and hypoxaemia with a PaO_2 <60 mmHg while breathing room air. All patients or their legally acceptable representatives provided written informed consent	for the current infection, or treatment with an investigational drug or device within the previous 30-day period was prohibited
Talbot, 2007 [22]	cSSSIs	(Ceftaroline 600 mg infused over 60 min q12h) vs. (i.v. standard therapy for 7–14 days). Subjects randomised to standard therapy initially received vancomycin (1 g q12h)	Adults >18 years with an SSSI requiring initial hospitalisation and treatment with i.v. antimicrobials were eligible for study participation if the SSSI involved deeper soft tissue and/or required significant surgical intervention (e.g. surgical or traumatic wound infection, major abscess, infected ulcer, or deep and extensive cellulitis) or had developed on a lower extremity in a subject with diabetes mellitus or well documented peripheral vascular disease. Subjects were further required to	Reasons to exclude subjects from participation included hypersensitivity reactions to any β-lactam antibiotic or vancomycin, history of red man syndrome or epilepsy, more than a single prior dose of a non-study antimicrobial within 96 h prior to randomisation unless there was clear evidence of failure, suspected anaerobic pathogens or *Pseudomonas aeruginosa*, ischaemic ulcer due to peripheral vascular disease, decubitus ulcer, diabetic foot ulcer present for >7 days, third-degree burn or a burn covering more than 5% of the total body surface area, human or animal bites, necrotizing fasciitis, AIDS, or any significant or life-threatening organ or systemic condition or

			have at least two local signs of cSSSI (purulent or seropurulent drainage/discharge, erythema, fluctuance, heat/localised warmth, pain/tenderness to palpation, swelling/induration) plus at least one systemic sign (oral temperature of >38 °C, WBC count >10 000/mm^3, >10% immature neutrophils)	disease. In addition, pregnant or nursing women or those of childbearing potential not using highly effective birth control were excluded from the study
Malangoni, 2006 [23]	cIAIs	(Sequential i.v. to p.o. moxifloxacin) vs. (i.v. piperacillin/tazobactam followed by p.o. amoxicillin/clavulanic acid)	Hospitalised patients ≥18 years were eligible for enrolment if they had a known or suspected cIAI plus anticipated treatment duration of ≥5 days. Patients had to be scheduled for a laparotomy or percutaneous aspiration and meet at least three of the following five criteria: fever (>38.5 °C rectal, >37.0 °C axillary, >37.5 °C oral/tympanic); leukocytosis (WBC count ≥12 000 cells/mm^3); symptoms referable to the abdominal cavity	Patients with any of the following diagnoses were excluded from the study: pre-existing ascites with spontaneous bacterial peritonitis; pancreatic origin of infection; perforated peptic ulcer or traumatic upper gastrointestinal tract perforation of <24 h duration; traumatic perforation of the small or large bowel of <12 h duration; transmural necrosis of the intestine owing to acute embolic, thrombotic or obstructive occlusions; acute cholecystitis with infection confined to the gallbladder; non-perforated appendicitis (unless there was evidence of an abscess or peritonitis);

		(e.g. anorexia, nausea, vomiting, pain); signs of IAI, e.g. tenderness (± rebound), involuntary guarding, absent or diminished bowel sounds, or abdominal wall rigidity; radiological evidence of gastrointestinal perforation or localised collections of potentially infected material. In addition, percutaneous aspiration had to show purulent material from the abdominal cavity or laparotomy had to reveal one or more of the following: gross peritoneal inflammation with purulent exudates; intra-abdominal abscess; or macroscopic contamination with gastrointestinal perforation. Patients with cIAI included those with: intra-abdominal abscess; secondary bacterial peritonitis;	perinephric infections; gynaecological infections; indwelling peritoneal catheter; planned multiple laparotomies; conditions requiring antibiotic irrigations of the abdominal cavity or incision; and patients requiring 'open abdomen' or marsupialisation (defined as planned repacking or planned debridement) techniques for management. Additionally, patients who were pregnant or nursing and patients with any of the following medical conditions were excluded from the study: immunological compromise, including those receiving chronic immunosuppressant therapy (>15 mg/day systemic prednisone or equivalent) or HIV-seropositive with a CD4 count <200 cells/μL; neutropenia (<1000 cells/μL); renal insufficiency (serum creatinine ≥2.5 mg/dL) or the need for haemodialysis or peritoneal dialysis; severe hepatic insufficiency (Child–Pugh class C); known QTc prolongation or receiving medications known to increase the QTc interval;

			appendicitis with evidence of a perforation or abscess (duration of symptoms >24 h); acute perforations of the stomach or duodenum if not operated on within 24 h of perforation; traumatic perforation of the small bowel (excluding the duodenum) or large bowel if not operated on within 12 h of perforation; small bowel (excluding duodenum) or large bowel perforation unrelated to trauma; and IAIs related to previous intra-abdominal operations	uncorrected hypokalaemia; known hypersensitivity to study drugs or multivitamin infusion; pre-existing hypervitaminosis; history of phenylketonuria; history of fluoroquinolone-associated tendinopathy; or infection requiring treatment with an anti-infective agent other than the study drugs. Patients who received prior antibiotic therapy were excluded unless therapy failed and they had a subsequent positive culture
Finch, 2002 [24]	CAP requiring initial parenteral treatment	(Sequential i.v. + p.o. moxifloxacin) vs. (sequential i.v. + p.o. co-amoxiclav with or without clarithromycin)	Patients >18 years with radiological evidence of CAP (and who had been in a hospital for <48 h). To be included, patients were required to have a temperature ≥38.5 °C or leukocytosis and at least one of the following clinical symptoms of pneumonia: cough;	Presence of a coexisting disease considered likely to affect the outcome of the study (e.g. lung cancer, empyema or severe cardiac failure) or a rapidly fatal underlying disease; known prolongation of the QT interval or the use of class IA or class III antiarrhythmics; known hypersensitivity to fluoroquinolones, β-lactams or macrolides; aspiration

			purulent sputum; dyspnoea; rigors; pleuritic chest pain; or auscultatory findings. All patients required initial parenteral therapy and approximately one-half had severe pneumonia, as defined by the criteria of the American Thoracic Society. To meet the definition of severe CAP the patients had to have at least one of the following: respiratory rate ≥30 breaths/min; hypoxaemia with a PaO_2 of ≤8 kPa (60 mmHg); a need for mechanical ventilation; diastolic blood pressure ≤60 mmHg; chest X-ray showing bilateral or multilobar involvement; or a requirement for treatment with vasopressors for >4 h	pneumonia; and pre-treatment with systemic antibacterial agents for >24 h prior to enrolment in the study. Patients who had clearly failed previous antibacterial therapy, which they had received for ≥72 h for the current pneumonia episode, could be enrolled unless the antibacterial regimen contained a fluoroquinolone or a β-lactam/β-lactamase inhibitor combination
Sher, 2002 [25]	ABS	(Gatifloxacin 400 mg qd for 5 days) vs. (gatifloxacin 400 mg qd for 10 days) vs.	Adults >18 years with a clinical diagnosis of acute, uncomplicated maxillary sinusitis	Patients with a chronic presentation (signs and symptoms for >28 days) of the current episode of sinusitis or complicated sinusitis

		(amoxicillin/clavulanic acid 875 mg b.i.d. for 10 days)	based on their medical history, physical examination, presence of signs and symptoms for ≥7 days and radiographic findings. They must have had facial pain/tenderness over one or both maxillary areas and purulent discharge from the maxillary sinus orifice, nose or back of the throat. Clinical diagnosis of sinusitis must have been confirmed radiographically through observation of opacification, an air/fluid level or mucosal thickening of >5 mm in one or both maxillary sinuses	(e.g. Pott's puffy tumour, malignancy involving the sinus, osteomyelitis, contiguous bone infection or necessity for reconstructive surgery) were excluded from the study, as were those with an anatomic abnormality involving the maxillary sinus ostium, a history of recent sinus surgery (within 3 months before enrolment) or nosocomial sinusitis secondary to head trauma or nasotracheal intubation. Patients with CF, significant hepatic disease (serum aminotransferase or total bilirubin levels >3× ULN) or renal insufficiency (estimated/calculated CL_{Cr} <30 mL/min) were also considered ineligible. Additional exclusion criteria were pregnancy, lactation and compromised immune function
Alvarez-Lerma, 2001 [26]	Nosocomial pneumonia (NP) in ICU patients	(i.v. piperacillin 4 g + tazobactam 500 mg q6h) vs. (i.v. ceftazidime 2 g q8h). Amikacin 15 mg/kg was administered to both groups	Patients >18 years admitted to the ICU with: length of hospital stay >48 h without previous signs of infection; appearance of clinical signs and symptoms suggestive	Pregnant and breast-feeding women, patients with documented hypersensitivity to β-lactams or to the study drugs, renal failure (serum creatinine concentration >3.5 mg/dL or CL_{Cr} < 20 mL/min); with

			of NP; detection of new and persistent radiological infiltrates or extension of previous infiltrates unrelated to any other diagnosis; signs of respiratory failure requiring mechanical ventilation (PaO_2 <90 mmHg, with FiO_2 >40%); ICU admission	antibiotic treatment within 72 h before inclusion in the study that were active against causative pathogens of pneumonia (except for cases of poor clinical evolution); need for concomitant administration of antibiotics that were active against causative pathogens of pneumonia; treatment with probenecid; leukopenia (<1.0 $\times 10^9$/L) or thrombocytopenia (<50.0 $\times$ 10^9/L); liver dysfunction with increase of ALT, AST or total bilirubin >3× ULN; massive bronchoaspiration of intestinal content. Patients with a life expectancy of <1 month and those with an order of no cardiopulmonary resuscitation in case of cardiac arrest
Siami, 2001 [27]	Severe SSTIs	(Clinafloxacin 200 mg i.v. q12h) vs. (piperacillin/tazobactam 3.375 g i.v. q6h)	Adult patients with severe or limb-threatening SSTIs serious enough to require hospitalisation and i.v. therapy + patients with acute (≤5 days prior) physical findings of complicated SSTI of bacterial aetiology and a	Pregnancy/breastfeeding, significant hepatobiliary or renal dysfunction (total bilirubin 3× ULN, ALT or AST levels 5× ULN or estimated CL_{Cr} of 20 mL/min). Immunodeficiency conditions, risk of convulsive disorders, hypersensitivity to study medications, septic shock, infected

			diagnosis of spontaneous infection (e.g. phlegmon, cellulitis, lymphangitis), wound infections (e.g. trauma wound, surgical wound) or diabetic foot infection. Patients were also required to have material available for culture	burns or decubitus ulcers, osteomyelitis and major amputation. Also, patients were not allowed to have: (i) been treated with more than a single dose of systemic antibacterial therapy for the current SSTI; (ii) had the infected site treated with topical antibiotics within 24 h prior to baseline culture collection; (iii) had prior treatment with any study medication within 7 days prior to study entry; or (iv) received treatment with any other investigational drug within 4 weeks prior to randomisation. Also excluded were patients: (i) receiving corticosteroids (>1 mg/kg body weight/day; (ii) requiring concomitant topical antimicrobial agents for SSTIs; (iii) receiving other antibacterial therapy for concomitant infections; and (iv) known to have SSTI pathogens resistant to any study medication
File, 2000 [28]	AECB	(p.o. gemifloxacin 320 mg qd for 5 days + p.o. amoxicillin/clavulanic acid–	Patients ≥40 years with a history of chronic bronchitis characterised by cough and	Serious underlying respiratory disease (such as pneumonia, CF, TB, bronchiectasis or active pulmonary

	placebo t.i.d.) vs. (p.o. amoxicillin/clavulanic acid 500/125 mg t.i.d. for 7 days + p.o. gemifloxacin–placebo for 5 days)	sputum production for >2 consecutive years and for most days in a period of 3 consecutive months. All patients required to have an acute exacerbation (defined as increased purulent sputum, cough and dyspnoea) suitable for treatment with an oral antibacterial	malignancies); a history of epilepsy, convulsions or myasthenia gravis; a history of haemolytic crisis or known G6PD deficiency; and presence of any other complicating infection, disease or condition that might compromise evaluation of the study drugs (such as HIV infection, renal impairment, abnormal liver function tests, and alcohol or drug abuse). Patients with known or suspected hypersensitivity to quinolones, penicillins or other β-lactam antibacterial agents; a history of tendonitis while taking fluoroquinolones. Pregnant or nursing women. Patients must not have received another antibacterial agent within 7 days of study entry, been treated with an investigational drug, vaccine or device within the past month or participated in a previous study of gemifloxacin. Concurrent use of sucralfate, probenecid or systemic steroids (>10 mg/day prednisolone or equivalent) was prohibited

Schouenborg, 2000 [29]	AECB	(Azithromycin 500 mg active tablets qd for 3 days + pivampicillin placebo tablets, b.i.d. for 10 days) vs. (pivampicillin 700 mg active tablets, b.i.d. for 10 days + azithromycin placebo tablets, qd for 3 days)	Ambulatory patients ≥18 years (with no upper age limit) with chronic bronchitis (defined as daily coughing and expectoration for more than 3 months within a 1-year period, and for 2 consecutive years without any other proven pulmonary disease) and with an acute exacerbation (indicated by two or more of the following: increase in dyspnoea; increase in coughing and expectoration; body temperature >38.5 °C)	Suspected pneumonia; need for parenteral antibiotic therapy; need for hospitalisation and/or oxygen support; terminal illness or other conditions precluding completion of the study or clinical evaluation; known hypersensitivity to macrolides or penicillins; pregnancy or lactation (women of childbearing potential were required to use adequate contraception). Treatment with another antimicrobial agent within 2 weeks (or with any investigational drug within 4 weeks of study entry); concomitant treatment with carbamazepine, cyclosporine, digoxin or ergotamine. Clinically significant hepatic or renal diseases (liver function tests more than 2× ULN and serum creatinine level >200 μmol/L); and any gastrointestinal disturbance that might affect study drug absorption
Cohn, 2000 [30]	cIAIs	(i.v. ciprofloxacin 400 mg q12h + metronidazole 500 mg q6h) vs. (i.v. piperacillin/tazobactam	Inpatients ≥18 years with cIAI requiring surgical intervention or percutaneous drainage in	Major reasons for exclusion from this trial included: allergy; renal insufficiency; an indwelling peritoneal catheter; ascites with

		3.375 g q6h)	addition to parenteral antibiotics were eligible for entry into the study	spontaneous bacterial peritonitis; abdominal infection secondary to acute pancreatitis; perforated peptic ulcer or traumatic upper gastrointestinal tract perforation of less than 24 h duration; and lower gastrointestinal tract perforation of less than 12 h duration. Patients were also excluded if their APACHE II score was >30, if they were not expected to survive 48 h, and if they had been given prior antibiotic therapy for this IAI episode for 24 h. Pregnant women or women who were breast-feeding were also excluded
Joshi, 1999 [31]	Nosocomial LRTI	All patients were to receive i.v. tobramycin administered at a dose of 5 mg/kg/day given in divided doses q8h. (piperacillin 3 g/375 mg q4h) vs. (ceftazidime 2 g administered q8h)	Hospitalised patients with a minimum age of 16 years, suffering from a clinically or bacteriologically confirmed diagnosis of hospital-acquired LRTI caused by bacteria thought to be susceptible to piperacillin/tazobactam and ceftazidime. Clinical criteria for enrolment	Patients were excluded in cases of: (a) known or suspected hypersensitivity to penicillins, cephalosporins, other β-lactam antibiotics, β-lactamase inhibitors or aminoglycosides; (b) moderate-to-severe renal dysfunction (CL_{Cr} 40 mL/min or serum creatinine 225 mmol/L); (c) haemodialysis, peritoneal dialysis, plasmapheresis or haemoperfusion; (d) evidence of active liver disease (serum

		included: recent onset of, or significant increase in, purulent sputum; temperature >38 °C; and/or a peripheral WBC count >10 × 10^9/L with >5% immature neutrophils. A pre-enrolment Gram stain of respiratory secretions must have shown >25 PMNs and <10 squamous epithelial cells per field at 100× magnification and a predominant pathogen. Female patients of childbearing potential must have had a negative pregnancy test within 48 h before enrolment into the study	transaminases, alkaline phosphatase or bilirubin >2× ULN; (e) peripheral granulocyte count 1 × 10^9/L or platelet count <50 × 10^9/L; more than two doses of another non-study antibacterial agent within 72 h before enrolment (unless this agent had proved to be clinically and bacteriologically ineffective); (f) recovery of a pathogen resistant to piperacillin/tazobactam, ceftazidime or tobramycin; (g) treatment with probenecid, presence of septic shock, CF, active or treated leukaemia, AIDS or known seropositivity for HIV antigen or antibody, active TB, lung cancer or metastatic lung disease or bronchial obstruction; (h) history of pneumonia, lung abscess, empyema or pleural effusion >500 mL; (i) administration of another investigational drug within 1 month before enrolment; (j) presence of concomitant infection other than hospital-acquired LRTI and associated bacteraemia; patients requiring PEEP ventilation >5 cm H_2O, patients

				requiring FiO_2 60% to maintain arterial haemoglobin oxygen saturation >90%; no bacterial pathogen in pre-treatment culture of sputum or other respiratory secretions within 72 h before enrolment; (k) any concomitant condition that could preclude evaluation of response or make it unlikely that the patient could complete the study
Brun-Buisson, 1998 [32]	VAP	(Piperacillin/tazobactam; 4/0.5 g q.i.d.) vs. (ceftazidime 1 g q.i.d.), both combined with amikacin (7.5 mg/kg b.i.d.)	Patients hospitalised for 72 h and having undergone mechanical ventilation for ≥48 h were eligible for inclusion in the study when clinically suspected of having VAP. Criteria for clinical suspicion of VAP included all of the following: clinical signs of sepsis (new fever, increase in temperature >38.2 °C or decrease <36.5 °C and increase in WBC count to >10 000/mm^3); purulent tracheal aspirates; and a new infiltrate or otherwise unexplained persistence or worsening of pre-	Patients were not eligible if they were diagnosed as having AIDS, a haematological malignancy or severe neutropenia (<500 PMNs/mm^3) or had a history of documented allergy to β-lactam antibiotics. Likewise, patients were not eligible: (i) if death was expected within 7 days of inclusion or a do-not-resuscitate order had been written; or (ii) if they had a severity score (SAPS II) on inclusion >50 and three or more organ failures or a rapidly fatal underlying disease. In addition, patients with suspected or documented TB, suspected or documented infection due to MRSA only, or a concomitant infection requiring other

			existing infiltrates on chest radiographs	antimicrobial therapy [or that had necessitated the recent (<48 h previously) introduction of antibiotics] were not eligible
Scheinin, 1994 [33]	Severe abdominal infections (Phase III study)	(Aspoxicillin 4 g i.v. drip infusions for ≤10 days) vs. (piperacillin 4 g q.i.d. i.v. drip infusions for ≤10 days)	Patients 16–91 years with suspected severe infections (either perforated appendicitis, acute cholecystitis, ulcer or colon perforation, or intra-abdominal abscess) requiring antimicrobial treatment	Pregnant women and patients with penicillin allergy, renal or liver insufficiency, recent antimicrobial treatment exceeding 24 h duration, or steroid treatment started within 10 days. Patients whose pathogens were resistant to the study drugs
Sweet, 1994 [34]	Pelvic infection in hospitalised women	(i.v. piperacillin 3 g + tazobactam 375 mg q8h) vs. (i.v. clindamycin 900 mg + gentamicin 2.5–5.0 mg/kg/day in divided doses q8h)	Non-pregnant women ≥16 years and hospitalised with a clinical diagnosis of endometritis, tubo-ovarian abscess, pelvic abscess, pelvic inflammatory disease, vaginal cuff infection or pelvic soft tissue infection who could provide informed consent	Patients with known hypersensitivity to any of the study drugs, renal dysfunction (serum creatinine >2.5 mg/dL or CL_{Cr} < 40 mL/min), hepatic dysfunction (transaminase, ALP or bilirubin >3× ULN), granulocyte count <1000/μL or platelet count <50 000/μL and those who had received more than two doses of an antibacterial agent within 72 h before enrolment. Also excluded were patients with: septic shock; gynaecological malignancies requiring surgery, chemotherapy or radiation therapy; CF, leukaemia, active

				TB, HIV infection or other concomitant non-gynaecological infections; pre-enrolment cultures revealing pathogens resistant to either of the study regimens, and any stage of syphilis without definitive treatment. Those expected to be discharged within 3 days were also non-eligible for inclusion
Klietmann, 1993 [35]	AECB	P.o.: [rufloxacin single dose 400 mg on Day 1 and single daily doses of 200 mg for subsequent 9 days] vs. [rufloxacin single dose 300 mg on Day 1 and single daily doses of 150 mg for subsequent 9 days] vs. [amoxicillin at 500 mg (one capsule) t.i.d. for 10 days]	Adults ≥18 years, outpatients of either sex seen at 23 German outpatient and 10 English general practice centres with a presumptive diagnosis of bacterial AECB	Life-threatening disease or any other infection requiring the use of systemic antibiotics, known hypersensitivity to quinolones or penicillins, administration of another antimicrobial agent within 7 days before admission, no use of contraceptive methods in women of childbearing potential, and pregnancy or nursing. Also excluded were patients with a serum creatinine level of >2 mg/dL, serious liver dysfunction (AST or ALT levels >2× ULN and/or serum bilirubin >1.5× ULN) or severe central nervous system disturbances
Brambilla, 1992 [36]	LRTIs	(Cefuroxime 750 mg by slow i.v. injection or infusion t.i.d. for	Adult hospitalised patients requiring initial i.v. antibiotic	Patients excluded were those known to be hypersensitive to penicillins or

		48–72 h, followed by cefuroxime axetil tablets 500 mg b.i.d. for at least 5 days) vs. (amoxicillin/clavulanic acid similarly as 1.2 g t.i.d. i.v. followed by 625 mg t.i.d. p.o.)	therapy for pneumonia or AECB or bronchiectasis were entered. Pneumonia was defined as an acute LRTI associated with fever and focal signs of infection on examination, confirmed radiographically by new (previously unrecorded) pulmonary infiltrates. Acute infective exacerbations of chronic bronchitis or bronchiectasis were defined as an increase in the symptoms of cough and dyspnoea, along with an increase in the volume and purulence of sputum, in the absence of any new (previously unrecorded) pulmonary infiltrates	cephalosporins, those who had received antibiotic therapy during the previous 48 h unless they had clinically failed to respond, those from whom pathogens resistant to the study drugs were isolated prior to entry, and those who were considered terminally ill or required assisted ventilation. Patients with bronchial carcinoma, pulmonary TB, atypical pneumonia (due to *Legionella* or mycoplasma) or left ventricular failure were also excluded, as were pregnant or breast-feeding women. Patients could only be entered once
Lousbergh, 1992 [37]	Respiratory tract infections	(150 mg roxithromycin tablets) vs. [amoxicillin (500 mg)/clavulanic acid tablets]	Patients >18 years with clinical signs of upper or LRTI	Pregnant or lactating women, those with a history of hypersensitivity to macrolides or β-lactams, or those known to have severe hepatic or renal insufficiency. Patients with other clinically significant

		abnormal findings (including abnormal laboratory results) that might affect interpretation of the results, and patients unable to comply with the protocol. Patients receiving cyclosporine or ergot derivatives or any drug affecting absorption of the study drugs were not included

TB, tuberculosis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; HIV, human immunodeficiency virus; RSV, respiratory syncytial virus; LRTI, lower respiratory tract infection; p.o., oral; RDAI, respiratory distress assessment index; CL_{Cr}, creatinine clearance; i.v., intravenous; ANC, absolute neutrophil count; CAP, community-acquired pneumonia; AECB, acute exacerbation of chronic bronchitis; WBC, white blood cell; ABS, acute bacterial sinusitis; CF, cystic fibrosis; CT, computed tomography; qd, once daily; b.i.d., twice daily; (c)IAI, (complicated) intra-abdominal infection; q8h, every 8 h; APACHE, Acute Physiology and Chronic Health Evaluation; AOM, acute otitis media; VAP, ventilator-associated pneumonia; CPIS, clinical pulmonary infection score; PaO_2, partial oxygen pressure; MRSA, meticillin-resistant *S. aureus*; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; (c)SSSI, (complicated) skin and skin-structure infection; q12h, every 12 h; AIDS, acquired immune deficiency syndrome; ICU, Intensive Care Unit; q6h, every 6 h; FiO_2, fraction of inspired oxygen; SSTI, skin and soft-tissue infection; t.i.d., three times daily; G6PD, glucose 6-

phosphate dehydrogenase; q4h, every 4 h; PMNs, polymorphonuclear cells; PEEP, positive end-expiratory pressure; q.i.d., four times daily; SAPS, simplified acute physiology score.

[a] Numerical rating scale (0 = no pain; 10 = worst possible pain).