New antibiotics for paediatric use: A review of a decade of regulatory trials submitted to the European Medicines Agency from 2000-Why aren't we doing better?

New antibiotics for paediatric use: A review of a decade of regulatory trials submitted to the European Medicines Agency from 2000—Why aren't we doing better?

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Abstract

New initiatives have been introduced in Europe and the USA to encourage more rapid development of antibiotics. The need to ensure these new antibiotics can be safely used in children, and especially neonates, is important owing to high antimicrobial resistance in these patient groups. This review aims to determine what lessons can be learnt from the recent regulatory processes to speed up access to new medicines for children, focusing on antibiotics licensed for adults by the EMA since 2000. For the 11 newly approved antibiotics, 31 clinical trials enrolling children in Europe were identified. However, many of these trials included both adults and children but did not provide a subset analysis for paediatrics, limiting the relevance of their findings. Some studies have been prematurely terminated and others are apparently active but are still not yet recruiting patients. Among paediatric-specific studies, 18 evaluate safety and efficacy of new compounds, 4 are pharmacokinetic studies, but only 2 focus on neonates. Nearly all studies with an agreed Paediatric Investigation Plan have just started or are not yet recruiting. For most antibiotics, despite adult phase 3 studies being completed, with specific concerns for particular drugs already noted, it will take another 3–5 years before adequate prescribing information becomes available for paediatricians. Evidence from this review suggests that we could do better. Lessons should be learnt from paediatric antiretroviral development, with neonatal and paediatric pharmacokinetic, clinical trial and pharmacovigilance drug development programmes being run directly in parallel with adult studies—not a decade behind.

1. Introduction

The development of novel antibiotics is a key priority of antibacterial therapy in the 21st century. The US Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA) in Europe are responsible for the scientific evaluation of applications for marketing authorisation of medicinal products and for the approval of specific proposed clinical indications for each compound.

Appropriate use of antibiotic agents may minimise selective pressure on the emergence of drug-resistant strains [1] and [2]. The licensing and marketing of a drug occur at the end of a long development process, in which clinical trials represent the final critical stage [3].

In the paediatric setting, the number of clinical trials is very low compared with the adult population: both economic and ethical factors can discourage pharmaceutical companies in conducting trials on children [4]. The result is a potential delay in the authorisation of antibiotics for children and a consequent increase in off-label prescribing [5]. Moreover, given the paucity of information of new antibiotics in children, data on drug safety and tolerability are often extrapolated from adult studies, with the consequent risks of underestimating toxicity, inadequate dosages and clinical failures [6].

Important new initiatives have recently been introduced both in the USA and Europe to encourage earlier and more complete evaluation of new drug products in paediatrics. The ‘Paediatric Regulation’ is a new legislation governing the development and authorisation of medicines in children that was introduced in the European Union (EU) in 2007 [7]. It brought in the creation of a Paediatric Committee, within the EMA, that provides objective scientific opinions on required drug development plans submitted by pharmaceutical companies. Such Paediatric Investigation Plans (PIPs) are aimed at ensuring that the necessary data to support authorisation of the medicine for paediatric use are obtained through targeted studies [8]. Further initiatives are now proposed to enhance the more rapid development of antibiotics. This study therefore aimed to see what lessons can be learnt from the recent regulatory processes to speed up access to new medicines for children, focusing on antibiotics licensed for adults by the EMA since 2000.

2. Materials and methods

The Medline, EMBASE and Cochrane library databases were systematically searched from January 2000 to December 2012 to identify all published papers regarding prospective clinical trials on the use of new antibiotics in infants and children aged 0–17 years and involving European countries. Only new antibiotics that have been licensed in the EU for adult use were

considered. A cross-check on references of major articles reporting adult data was also performed. To identify ongoing trials or recently completed trials, a search of the World Health Organization (WHO), US National Institutes of Health and EU clinical trials registers was performed (last accessed 31 January 2013) [9], [10] and [11]. PIPs were systematically searched through the EMA database [8].

3. Results

Eleven antibiotics approved in the EU since 2000 were identified (Table 1). A total of 31 clinical trials were found. A brief summary of completed and ongoing trials, as well as PIPs, for each drug is given.

Table 1.

Antimicrobials licensed for the adult population in the European Union (EU) since 2000.

Drug	EU approved indications in adults	EU approved indications in children	Paediatric Investigation Plans (EU)
Aztreonam lysine	Pseudomonas aeruginosainfection in patients with cystic fibrosis	None	None
Ceftaroline fosamil	cSSTI, CAP	None	cSSTIs, CAP (0–18 years)
Daptomycin	cSSTI, Staphylococcus aureusbacteraemia, S. aureus right-sided endocarditis	None	None
Doripenem monohydrate	cIAI, cUTI, HAP	None	HAP/VAP, cIAI, UTI (0–18 years)
Ertapenem sodium	cIAI, CAP, cSSTI (diabetic foot), acute pelvic infection, surgical-site infection	cIAI, CAP, cSSTI (diabetic foot), acute pelvic infection	None

Drug	EU approved indications in adults	EU approved indications in children	Paediatric Investigation Plans (EU)
	prophylaxis in elective colorectal surgery	in children aged ≥3 months of age	
Fidaxomicin	CDAD	None	Safety and pharmacokinetics (2–17 years) Development of an age-appropriate oral suspension formulation (0–18 years)
Linezolid	HAP, CAP, cSSTI by Gram-negative bacteria	None	None
Moxifloxacin	Acute bacterial sinusitis, AECB, CAP	None	PID (12–18 years) cIAI (3 months to 18 years)
Retapamulin	Superficial SSTI (impetigo, infected small lacerations, abrasions or sutured wounds)	Superficial SSTI (impetigo, infected small lacerations, abrasions or sutured wounds) in children ≥9 months of age	None
Telithromycin	CAP (mild to moderate)	None	None
Tigecycline	cSSTI, cIAI	None	cSSTIs, cIAIs (8–18 years)

cSSTI, complicated skin and soft-tissue infection; CAP, community-acquired pneumonia; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; VAP, ventilator-associated

pneumonia; CDAD, Clostridium difficile-associated diarrhoea; AECB, acute exacerbations of chronic bronchitis; PID, pelvic inflammatory disease.

Table options

3.1. Aztreonam lysine

Aztreonam is a synthetic monobactam that has been available intravenously for many decades. It displays a mechanism of action similar to penicillin and has selective bactericidal activity against susceptible Gram-negative bacteria, including Pseudomonas aeruginosa and most clinically relevant Enterobacteriaceae. Aztreonam is inactivated by extended-spectrum β-lactamases (ESBLs) and has no activity against Gram-positive bacteria or anaerobes.

An inhaled formulation, aztreonam lysine (AZLI), administered using an ultrasonic nebuliser, was recently developed. It received conditional approval by the EMA in 2009 for the treatment of P. aeruginosa infections in adults with cystic fibrosis and was also approved by the FDA in 2010, although not in children [12] and [13]. Three clinical trials enrolling children with cystic fibrosis and lower respiratory tract infections with P. aeruginosa are registered in Europe (Table 2). AZLI demonstrated superiority in lung function and a reduction in acute pulmonary exacerbations compared with tobramycin inhalation solution in adult and paediatric patients with pulmonary P. aeruginosacolonisation. However, only a small number of children were enrolled (n = 58; 22%) and no separate analysis for the paediatric population was performed [14] and [15]. Two studies evaluating the safety and efficacy of AZLI are active but are not yet recruiting patients [16] and [17].

Table 2.

European clinical trials on aztreonam lysine involving paediatric patients.

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint	Main exclusion criteria	Comparator	Aztreonam dose/duration	Status	Results
NCT00757237[14] and [15]	Phase 3, RCT, OL	USA, Europe	268 (58 aged <18 years)	≥6 years	Pulmonary infection by Pseudomonas aeruginosa in pts with CF	Comparative safety and efficacy	–	Previous antipseudomonal treatment; lung transplantation; colonisation by Burkholderiaspp.; continuous oxygen supplementation; high-dose steroids	TNS 300 mg q12h as intermittent 28-day courses	Inhalation solution 75 mg q8h as intermittent 28-day courses	Completed	Mean relative changes after one course: AZLI, 8.35%; TNS, 0.55% (P < 0.001). Mean actual changes across three courses: AZLI, 2.05%; TNS,–0.66% (P = 0.002)

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint	Main exclusion criteria	Comparator	Aztreonam dose/duration	Status	Results
												Fewer respiratory hospitalisations (P = 0.044) and respiratory events requiring additional antipseudomonal antibiotics (P = 0.004) in AZLI-treated pts

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint	Main exclusion criteria	Comparator	Aztreonam dose/duration	Status	Results
NCT01375049[16]	Phase 2, OL	USA, Europe	80	3 months to 17 years	Lower respiratory tract infection by P. aeruginosa in pts with CF	Microbiological response	–	Previous antipseudomonal treatment; lung transplantation; colonisation by Burkholderiaspp.; continuous oxygen supplementation	None	Inhalation solution 75 mg q8h for 28 days	Active but not recruiting	NA
NCT01404234[17]	Phase 3, OL	USA, Europe	60	Up to 12 years	Chronic lower respiratory tract infection by P. aeruginosa in	Safety	Efficacy: improvement of respiratory functionality and changes in P.	Previous antipseudomonal treatment; lung transplantation; colonisati	None	Inhalation solution 75 mg q8h as three interm	Active but not recruiting	NA

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint	Main exclusion criteria	Comparator	Aztreonam dose/duration	Status	Results
					pts with CF		aeruginosae xacerbations and sputum density	on by Burkholderiaspp.		ittent 28-day courses		

pts, patients; RCT, randomised controlled trial; OL, open label; CF, cystic fibrosis; TNS, tobramycin nebuliser solution; q12h, every 12 h; q8h, every 8 h; AZLI, aztreonam for inhalation solution; NA, not available.

Table options

No PIP is currently agreed on AZLI.

3.2. Ceftaroline fosamil

Ceftaroline fosamil is a novel broad-spectrum cephalosporin approved by the EMA in 2012 for the treatment of adults with complicated skin and soft-tissue infections (cSSTIs) and community-acquired pneumonia (CAP) [18].

Ceftaroline inhibits bacterial cell wall synthesis by binding penicillin-binding proteins (PBPs), including PBP2a produced by meticillin-resistant Staphylococcus aureus(MRSA). It has activity against a wide spectrum of Gram-negative and Gram-positive pathogens, such as MRSA (including vancomycin- and daptomycin-resistant strains), penicillin-resistant Streptococcus pneumoniae (PRSP), meticillin-resistant Staphylococcus epidermidis (MRSE) and Enterococcus faecalis. It is not active against P. aeruginosa and ESBL-producing strains [19].

Although clinical data are still limited, ceftaroline displays a good safety and tolerability profile. The paediatric dosage is yet to be determined. In addition to the approved indications, a potential promising role for ceftaroline is empirical monotherapy when an MRSA or MRSE infection is suspected.

Two randomised controlled trials (RCTs) are recruiting paediatric patients in Europe (Table 3): they will assess the safety, efficacy, tolerability and pharmacokinetics of ceftaroline versus comparators in children aged 2 months to 18 years with CAP and cSSTIs [20] and [21].

Table 3.

European clinical trials on ceftaroline fosamil involving paediatric patients.

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Ceftaroline fosamil dose	Status
NCT01530763[20]	Phase 2–3, RCT, SB	USA, Europe	160 (estimated)	2 months to 18 years	CAP	Comparative safety and tolerability	Comparative efficacy; pharmacokinetics of ceftaroline fosamil in plasma and CSF	Hypersensitivity to β-lactams; infection with a pathogen resistant to ceftriaxone; sources of infection other than CAP; non-infectious causes of pulmonary infiltrates	Ceftriaxone i.v. 75 mg/kg/day (up to 4 g/day) divided q12h	≥6 months: i.v. ceftaroline fosamil 12 mg/kg (if ≤33 kg body weight) or 400 mg (if >33 kg body weight) q8h<6	Recruiting

										months: 8 mg/kg q8h	
NCT01400867[21]	Phase 2–3, RCT, SB	USA, Europe, South America, Asia, South Africa	270 (estimated)	2 months to 18 years	cSSTI	Comparative safety and tolerability	Comparative efficacy; pharmacokinetics of ceftaroline fosamil in plasma	Hypersensitivity to vancomycin, aztreonam or β-lactams; requirement for concomitant systemic antimicrobial therapy; history of seizures, excluding febrile seizure of childhood; signs or suspicion of meningitis	Vancomycin i.v. 15 mg/kg q6h or cefazolin i.v. 75 mg/kg/day divided q8h ± aztreonam i.v. 30 mg/kg q8h	≥6 months: ceftaroline fosamil i.v. 12 mg/kg (if ≤33 kg body weight) or 400 mg (if >33 kg body weight) q8h <6 months: 8 mg/kg q8h	Recruiting

pts, patients; RCT, randomised controlled trial; SB, single blind; CAP, community-acquired pneumonia; CSF, cerebrospinal fluid; i.v., intravenous; q12h, every 12 h; q8h, every 8 h; cSSTI, complicated skin and soft-tissue infection; q6h, every 6 h.

Table options

A PIP for treatment of cSSTI and CAP has been agreed [22].

3.3. Daptomycin

Daptomycin is a cyclic lipopeptide that was approved by the FDA in 2003 for the treatment of adults with SSTIs caused by Gram-positive bacteria as well as S. aureusbacteraemia or right-sided endocarditis. It is inactivated by pulmonary surfactants and therefore should not be used for non-haematogenous pneumonia [23] and [24].

Daptomycin binds to the bacterial cell membrane in a calcium-dependent manner, causing rapid membrane depolarisation and bacterial death. It has selective activity against Gram-positive bacteria, including glycopeptide-resistant enterococci, MRSA, MRSE, streptococci and corynebacteria. In adults, daptomycin is given intravenously at 4 mg/kg or 6 mg/kg once daily, respectively, for SSTIs and S. aureusbacteraemia/endocarditis. Safety and tolerability of higher dosages have been reported both in adults and children [25], [26] and [27]. Daptomycin is generally well tolerated. As its most relevant side effect is muscular toxicity, regular monitoring of creatine kinase levels is recommended [28]. A warning that daptomycin could cause life-threatening eosinophilic pneumonia has recently been issued [29].

The experience of daptomycin in children is very limited and the paediatric dosing regimen remains to be determined [30], [31], [32], [33], [34] and [35]. According to the latest Infectious Diseases Society of America (IDSA) guidelines on the management of MRSA infections, daptomycin should be administered at 6–10 mg/kg every 24 h in children with bacteraemia, osteomyelitis and septic arthritis [36].

The pharmacokinetic (PK) profile, efficacy and safety of daptomycin in infants and children are under evaluation in several trials. Among these, only two are recruiting children in the EU. One study aims at characterising the peak concentration of daptomycin in cerebrospinal fluid of children aged 3 months to 16 years with acute Gram-positive meningitis (Table 4); daptomycin will be given as single-dose add-on therapy [37]. The second study will describe the safety and efficacy of daptomycin versus standard of care in children aged 2–17 years with S. aureus bacteraemia [38].

Table 4.

European clinical trials on daptomycin (DAP) involving paediatric patients.

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint	Main exclusion criteria	Daptomycin dose/duration	Comparators	Status
NCT01522105[37]	OL, SGA, phase 1	Europe	5 (estimated)	3 months to 16 years	Gram-positive meningitis	Characterisation of peak concentration of DAP in the CSF	Evaluate possible side effects of DAP	Gram-negative bacteria in the CSF; renal impairment; CK level >2× upper age-related norm or muscular disease/weakness; allergy or hypersensitivity to DAP; known significant chronic	One i.v. dose (3–24 months, 6 mg/kg; 2–6 years, 10 mg/kg; 7–11 years, 8 mg/kg; 12–16 years, 6 mg/kg) given 24 h after first	None	Recruiting

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint	Main exclusion criteria	Daptomycin dose/duration	Comparators	Status
								diseases; underlying neurological disease with disruption of blood–brain barrier; epilepsy, peripheral neuropathy, Guillain–Barré syndrome	ceftriaxone dose		
NCT01728376[38]	RCT, SB, phase 4	USA, Europe, South America, Asia	75 (estimated)	2–17 years	Staphylococcus aureusbacteraemia	Comparative safety	Comparative efficacy	Shock or hypotension unresponsive to standard therapy; intoleranc	DAP i.v. at 7 mg/kg (age 12–17 years), 9 mg/kg (age	Vancomycin, semisynthetic penicillin, first-generation	Recruiting

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint	Main exclusion criteria	Daptomycin dose/duration	Comparators	Status
								e or hypersensitivity to DAP; renal insufficiency; rhabdomyolysis; or significant CK elevation; history of clinically significant muscular disease, nervous system or seizure disorder; S. aureuspneumonia,	7–11 years), 12 mg/kg (ages 2–6 years)	cephalosporin, clindamycin	

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint	Main exclusion criteria	Daptomycin dose/duration	Comparators	Status
								empyema, meningitis or endocarditis			

pts, patients; OL, open label; SGA, single group assignment; CSF, cerebrospinal fluid; CK, creatine kinase; i.v., intravenous; RCT, randomised controlled trial; SB, single blind.

Table options

At present, the lack of adequate safety data does not allow daptomycin to be routinely used in children. Potential uses in selected cases include right-sided endocarditis with or without bacteraemia, infection of intravascular devices, and osteoarticular infections caused by MRSA, MRSE and vancomycin-resistant enterococci (VRE) [39].

No PIP is currently agreed on daptomycin.

3.4. Doripenem monohydrate

Doripenem monohydrate is the most recently developed carbapenem [40] and [41]. It was approved by the EMA in 2008 for the treatment of nosocomial pneumonia (NP) [including ventilator-associated pneumonia (VAP)], complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs) including pyelonephritis.

When compared with imipenem/cilastatin and meropenem, doripenem had enhanced in vitro activity against P. aeruginosa and Acinetobacter spp. It is also active against most β-lactam-susceptible Gram-positive bacteria, Gram-negative bacteria (including ESBL-producing strains) and anaerobes. As with other carbapenems, it inhibits synthesis of the bacterial

cell wall by attaching to PBPs and has no activity against Stenotrophomonas maltophilia. Adverse effects of doripenem are similar to those of other carbapenems [40], [41], [42], [43] and [44].

In phase 3 studies, doripenem was non-inferior to comparators in the treatment of NP and cIAIs [45], [46] and [47]. However, a recent trial evaluating its safety and efficacy in severely ill patients with VAP was terminated prematurely due to excess mortality and poorer clinical cure rates in the doripenem group [48]: in that study, doripenem was administered at a higher dose [1 g every 8 h (q8h)] and for a shorter treatment period (7 days) than currently authorised (500 mg q8h for 10–14 days) and was compared with 1 g q8h of imipenem/cilastatin for 10 days. Following these preliminary results, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended updating the prescribing information allowing higher doses (1 g q8h for 10–14 days) in patients with NP caused by non-fermenting Gram-negative bacteria [49].

PK and pharmacovigilance studies of doripenem in children have been started in Europe (Table 5).

Table 5.

European clinical trials on doripenem monohydrate involving paediatric patients.

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Doripenem dose/duration	Status	Results
NCT01381848, EudraCT 2009-014387-20 [50] and [51]	Phase 1, OL	USA, Europe	48	0–12 weeks	Bacterial infection	PK study (doripenem concentrations in blood	Safety of single-dose doripenem	Clinically significant abnormal physical examination, vital signs or laboratory	None	Single i.v. dose: 5 mg/kg in pts <8 weeks; 8 mg/kg in	Completed	NA

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Doripenem dose/duration	Status	Results
						samples)		testing at screening		pts ≥8 weeks		
NCT01110421, EudraCT 2009-016069-27 [52] and [53]	Phase 3, RCT, DB	South and Central America, USA, Europe, Asia	140	3 months to 18 years	CAP	Comparative safety	Clinical cure at TOC and EOT; relapse at LTFU; population PK analysis	Suspected or proven study drug-resistant organisms (e.g. Staphylococcus aureus, Stenotrophomonas, etc.); immunosuppression (ANC <500 cells/μL); epilepsy	Cefepime i.v. (50 mg/kg up to 2 g/dose q8h) for ≥3 days, followed by PO amoxicillin/clavulanate potassium or other PO antibiotics (total 10–14 days)	20 mg/kg i.v. up to 500 mg/dose q8h for ≥3 days, followed by PO amoxicillin/clavulanate potassium or alternative PO antibiotic therapy (total 10–14 days)	Suspended	NA

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Doripenem dose/duration	Status	Results
NCT01110408, EudraCT 2009-015953-18 [54] and [55]	Phase 3, RCT, DB	USA, Europe, Asia, South America, Africa	140	3 months to 18 years	cUTI	Comparative safety	Clinical cure and microbiological response at TOC and LTFU; clinical improvement and microbiological response at EOT; population PK analysis	Concomitant infections; diagnosis of intractable UTI, permanent urinary catheter, abscesses; suspected or proven study drug-resistant organisms; ANC <500 cells/μL; epilepsy	Cefepime i.v. (50 mg/kg up to 2 g/dose q8h) for 3–14 days. Pts may be discharged with PO antibiotic therapy	20 mg/kg i.v. up to 500 mg/dose q8h for 3–14 days. Pts may be discharged with PO antibiotic therapy	Recruiting	NA

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Doripenem dose/duration	Status	Results
NCT01110382, EudraCT 2009-015864-32 [56] and [57]	Phase 3, RCT, DB	USA, Europe, South America	140	3 months to 18 years	cIAI	Comparative safety	Clinical cure and microbiological response at TOC and LTFU; clinical improvement at EOT; population PK analysis	Concomitant infections; abdominal wall abscess; suspected or proven study drug-resistant organisms; ANC <500 cells/μL; epilepsy	Meropenem 20 mg/kg i.v. up to 1 g/dose q8h for 3–14 days. i.v. drugs may be switched to a PO antibiotic to complete the 5–14-day course of treatment	20 mg/kg i.v. up to 500 mg/dose q8h for 3–14 days. i.v. drugs may be switched to an oral antibiotic to complete the 5–14-day course of treatment	Recruiting	NA
NCT01366651[58]	Phase 1,	Europe	10	0–1 year	Meningitis	PK study (doripenem concen	Safety of doripenem	Any condition that may interfere with the assessment,	None	Pts <12 weeks, 10 mg/kg i.v. q8h for 5 doses; pts	Recruiting	NA

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Doripenem dose/duration	Status	Results
	OL					trations in CSF and plasma)		according to investigator		≥12 weeks to <1 year, 30 mg/kg i.v. q8h for 5 doses		

pts, patients; OL, open label; PK, pharmacokinetic; i.v., intravenous; NA, not available; RCT, randomised controlled trial; DB, double blind; CAP, community-acquired pneumonia; TOC, test of cure; EOT, end of i.v. therapy; LTFU, long-term follow-up; ANC, absolute neutrophil count; q8h, every 8 h; PO, per os; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; CSF, cerebrospinal fluid.

Table options

The pharmacokinetics, safety and tolerability of single-dose doripenem have been studied in hospitalised neonates (both term and preterm) and in infants <12 weeks of age with, or at risk for, bacterial infections under treatment with other intravenous (i.v.) antibiotics [50] and [51]. In that study, doripenem was given as add-on therapy. The study was completed in April 2012 but results are not available at present. One study comparing the safety and tolerability of doripenem with cefepime in children with bacterial pneumonia was suspended following premature discontinuation of the adult VAP study [52] and [53]. Three randomised controlled paediatric studies are currently ongoing. Doripenem is compared with i.v. cefepime for safety and efficacy in the treatment of cUTIs in children aged 3 months to 18 years; sampling for PK investigation is scheduled in doripenem-treated subjects [54] and [55]. A second study is evaluating doripenem versus meropenem in hospitalised children with cIAIs; a PK subanalysis for the doripenem group is also planned [56] and [57]. Another study plans to assess the penetration of doripenem (given as add-on therapy) into the cerebrospinal fluid of hospitalised children aged <1 year with meningitis [58].

Following the limited data on the safety of doripenem and its limited potential advantages over older carbapenems, its role in paediatrics remains to be established. Given its broad spectrum of activity, it might be useful for treating children with nosocomial infections or with infections caused by enteric or non-fermentative Gram-negative bacteria [41].

A PIP for treatment of hospital-acquired pneumonia (HAP)/VAP, cIAIs and UTIs including complicated and uncomplicated pyelonephritis and cases with concurrent bacteraemia has been agreed [59].

3.5. Ertapenem sodium

Ertapenem is a carbapenem with broad-spectrum antibacterial activity against aerobic and anaerobic pathogens, including ESBL- and AmpC-producing Gram-negatives [60] and [61]. In contrast to other carbapenems, it is not active against P. aeruginosa and Acinetobacter baumannii. Ertapenem is approved in Europe for the treatment of adults and children aged ≥3 months with cIAIs, CAP, diabetic foot infections and acute pelvic infection. It is also licensed for surgical-site infection prophylaxis in elective colorectal surgery in adults. Further indications in the USA include cSSTIs and UTIs [62]. Paediatric dosing is 15 mg/kg i.v. every 12 h (q12h) in children aged 3 months to 12 years (maximum 1 g/daily) and 1 g once daily in older children [60]. The intramuscular route has been licensed in the USA but not in Europe. The safety profile in children was comparable with that found in adults [60]. Use of ertapenem was associated with neutropenia, diarrhoea and mild-to-moderate elevation of liver function tests; seizures were identified with comparable frequency to comparators [63].

Arguedas et al. investigated the safety, tolerability and efficacy of ertapenem versus ceftriaxone in children aged 3 months to 17 years with cUTIs, SSTIs or CAP (Table 6) [64] and [65]. The overall incidence of clinical adverse events (AEs) was comparable between the two groups. The most common drug-related AEs were diarrhoea, vomiting, infusion-site pain and erythema. In general, the clinical response to ertapenem was similar to that found in adults for similar infections.

Table 6.

European clinical trials on ertapenem sodium involving paediatric patients.

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Ertapenem dose/duration	Status	Results
NCT00451386 [64] and [65]	Phase 3, RCT	Europe, USA, South America	403	3 months to 17 years	cUTI, CAP, SSTI	Comparative safety (incidence of clinical and laboratory drug-related serious AEs)	Comparative tolerability and efficacy	Infected burn wounds; necrotising fasciitis; osteomyelitis or septic arthritis; mechanical ventilation; cystic fibrosis; chronic lung disease or empyema; significant renal impairment	Ceftriaxone	13–17 years, 1 g i.v. OD; 3 months–12 years, 15 mg/kg BID (maximum 1 g daily) for a mean of 4 days	Completed	Most common drug-related clinical AEs: diarrhoea (5.9% ertapenem, 10% ceftriaxone), infusion-site erythema (3% ertapenem,

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Ertapenem dose/duration	Status	Results
												2% ceftriaxone), infusion-site pain (5% ertapenem, 1% ceftriaxone). Serious drug-related clinical AE: 1 pt each. No seriou

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Ertapenem dose/duration	Status	Results
												s drug-related laboratory AEs. Overall clinical response to ertapenem similar to larger clinical trials in adults

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Ertapenem dose/duration	Status	Results
NCT01069900, EudraCT 2009-015578-37 [66] and [67]	RCT, DB, phase 3	Europe, South America, USA, South/East Asia	300	3 months to 17 years	IAI	Comparative safety with a special focus on cardiac and musculoskeletal events	Evaluation of musculoskeletal AEs; evaluation of electrocardiogram profiles obtained on Days 1 and 3 pre treatment and post treatment; clinical response at TOC and EOT; bacteriol	Spontaneous bacterial peritonitis; all pancreatic processes; early acute or suppurative (non-perforated) appendicitis; known severe immunosuppression; congenital or acquired QT prolongation;	Moxifloxacin	1 g i.v. OD (age 13–18 years) or i.v. 15 mg q12h, max 1 g daily (age <13 years) for 3–14 days	Recruiting	NA

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Ertapenem dose/duration	Status	Results
							ogical response at Days 3–5 and EOT	concomitant treatment with QT prolonging drugs; history of tendon disease/disorder related to quinolone treatment; abnormal musculoskeletal findings at baseline				

pts, patients; RCT, randomised controlled trial; cUTI, complicated urinary tract infection; CAP, community-acquired pneumonia; SSTI, skin and soft-tissue infection; AE, adverse event; i.v., intravenous; OD, once daily; BID, twice daily; DB, double blind; IAI, intra-abdominal infection; TOC, test of cure; EOT, end of therapy; q12h, every 12 h; NA, not available.

Table options

In a separate RCT, ertapenem was the comparator drug to moxifloxacin in children aged 3 months to 17 years with cIAIs [66] and [67].

A potential advantage of ertapenem compared with other carbapenems is the spectrum of activity sparing P. aeruginosa: ertapenem does not adversely affect carbapenem resistance among these bacteria, and improved P. aeruginosa susceptibilities have been reported after years of its use [61] and [68]. Ertapenem's prolonged half-life with once-daily dosing facilitates its use in outpatient parenteral antibiotic therapy (OPAT) for children older than 12 years.

No PIP is currently available on ertapenem.

3.6. Fidaxomicin

Fidaxomicin is the first in a new class of narrow-spectrum 18-ring macrolide antibiotics. Produced by an actinomycete, it has selective bactericidal activity against pathogenic Clostridium difficile, with minimal effects on the normal intestinal microflora. Its mechanism of action consists in inhibition of bacterial RNA polymerase [69] and [70].

Fidaxomicin is approved in the EU and USA for the treatment of adults with C. difficile-associated diarrhoea (CDAD). In pre-marketing studies, fidaxomicin was non-inferior to oral vancomycin in achieving clinical cure of CDAD (92.1% vs. 89.8%) and was associated with fewer recurrences [71]. In the USA, a study on the safety, tolerability and pharmacokinetics of fidaxomicin in children (6 months to 18 years) with CDAD is currently in progress [72]. In the EU, a prospective observational study in children has recently started (Table 7), aiming to determine the incidence and clinical outcomes of C. difficile infection in 60 term neonates and to investigate the feasibility of a potential interventional study [73].

Table 7.

European clinical trial on fidaxomicin involving paediatric patients.

Study no.	Study type	Location	No. of pts	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Status
NCT01533844 [73]	Observational, non-interventional	Europe	60 (estimated)	0–27 days	CDAD	To determine the feasibility of a potential interventional study with fidaxomicin; to determine the incidence and clinical aspects of CDI in neonates and whether a subgroup can be identified	–	Preterm neonates; negative Clostridium difficiletoxin test	Recruiting

Study no.	Study type	Location	No. of pts	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Status
						where treatment with fidaxomicin therapy might improve outcome			

pts, patients; CDAD, Clostridium difficile-associated disease; CDI, C. difficile infection.

Table options

A PIP for treatment of CDAD in children has been agreed [74].

3.7. Linezolid

Linezolid is the first member of the oxazolidinones [75]. It exhibits a selective spectrum of activity against Gram-positive bacteria, including MRSA, MRSE, VRE and PRSP. Linezolid inhibits bacterial protein synthesis through blocking the initiation process.

In Europe, approved indications for its use in adults are CAP, HAP and cSSTIs caused by Gram-positive bacteria. The FDA labelled linezolid for paediatric use in 2002 at doses of 10 mg/kg q8h in children aged 0–11 years and 10 mg/kg q12h (maximum 600 mg q12h) in older children. Conversely, in most European countries it remains off-label in the paediatric setting, although recent reports note that it is occasionally prescribed in children [76] and [77]. Neonatal dosing of linezolid has been poorly studied. PK data suggest that linezolid clearance is decreased in preterm and in term neonates <7 days of age; therefore, all neonates should be treated with 10 mg/kg q12h during their first week of life [78]. The main side effects in

children are gastrointestinal disturbances. Peripheral and optic neuropathy and myelotoxicity seem less frequent than in adults, however the risk of these severe complications should be considered and careful monitoring is recommended [77]. Linezolid has several advantages over glycopeptides. The high and rapid tissue penetration supports its use for central nervous system or osteoarticular infections. The oral formulation, with excellent bioavailability, can be useful in step-down therapy and in outpatients. Its activity against mycobacteria justifies its potential role in treating drug-resistant tuberculosis [79].

Five clinical trials enrolling adults and children (aged 13–17 years) treated with linezolid have been completed in the EU (Table 8). In three trials, linezolid was administered to treat CAP caused by PRSP, cSSTIs and catheter-related bloodstream infections due to Gram-positive organisms, or febrile neutropenia in oncological patients [80], [81], [82], [83] and [84]. In all these studies the number of enrolled children was limited and a stratified analysis for the paediatric population was not given. Therefore, no definite conclusions can be drawn. For the remaining two trials, evaluating children aged 0–17 years with haemato-oncological disease or undergoing haematopoietic stem cell transplantation, results are not yet available. The first study evaluated the efficacy and safety of rescue therapy with antibiotic-lock technique with either linezolid, vancomycin or amikacin for the treatment of indwelling central venous catheter (CVC)-related bacteraemia in retained CVC [85]. The second study evaluated continuous infusion with either linezolid, vancomycin, ceftazidime or meropenem as salvage therapy of tunnel/pocket infections of an indwelling CVC [86].

Table 8.

European clinical trials on linezolid (LNZ) involving paediatric patients.

Study no.	Study type	Locations	No. of pts (ITT)	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Comparator(s)	Linezolid dose/ duration	Status	Results
NCT00035269[80]	Phase 3, not contr	Europe, USA	229	14–96 years (mea	CAP by Streptococcus pneumoniae	Microbiological	Clinical efficac	Previous treatment for	None	600 mg q12h i.v./P	Completed	Clinical success,

Study no.	Study type	Locations	No. of pts (ITT)	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Comparator(s)	Linezolid dose/ duration	Status	Results
	olled, OL	, Asia		n 54.5 years)		efficacy	y and safety	>24 h with another antibiotic; HIV-positive subjects; low CD4 count		O for 10–21 days		77.3%. Microbiological eradication, 84.3%. Main AEs, abdominal pain (3.5%), headache (3.9%), diarrhoea (4.4%), nausea (5.7%), anaemia

Study no.	Study type	Locations	No. of pts (ITT)	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Comparator(s)	Linezolid dose/duration	Status	Results
												(3.1%), insomnia (3.5%)
NCT00037050, EudraCT: 2004-001511-54 [81], [82] and [83]	Phase 3, RCT, OL	Europe, USA, Latin America, South America, Asia, Russian Federation, South	363 LNZ, 363 comparator	LNZ, 16–92 years (mean 53.7); comparator, 14–94 years (mean 53.8	Central indwelling catheter-related cSSTI or bacteraemia by Staphylococcus aureus, CoNS, Enterococcusspp.	Evaluate empirical treatment	Comparative efficacy of LNZ; incidence of late metastatic sequelae in patients treated with LNZ	Tunnelled catheter that cannot be removed; endocarditis; infection of permanent intravascular device	Vancomycin i.v. 1 g q12h; oxacillin i.v. 2 g q6h; dicloxacillin PO 500 mg q6h	600 mg q12h i.v./PO for 10–28 days	Completed	Clinical success: cSSTIs, 77.8% LNZ, 77.9% comparator; bacteraemia, 75.3% LNZ, 80.8% comparator Microb

Study no.	Study type	Locations	No. of pts (ITT)	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Comparator(s)	Linezolid dose/ duration	Status	Results
		Africa		years)				s; previous antibiotic treatment for >24 h; patients with HIV and low CD4 count				iological eradication: cSSTIs, 89.6% LNZ, 89.9% comparator; bacteraemia, 86.3 5 LNZ, 90.5% comparator
NCT00035425 [84]	Phase 3, RCT, DB	Europe, USA, Latin	61 LNZ, 57 com	LNZ, 15–80 years (mea	Suspected or proven Gram-positive (S. aureus,	Comparative clinical	Microbiological	Fever due to known causes	Vancomycin 1 g	600 mg q 12 h i.v. for	Completed	Clinical success: 82.9%

Study no.	Study type	Locations	No. of pts (ITT)	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Comparator(s)	Linezolid dose/ duration	Status	Results
		America, Asia	parator	n 45.2 years)	CoNS, Streptococcussp.) infection in febrile, neutropenic cancer pts	efficacy	outcome	; HIV infection; recent bone marrow transplant; non-removable infected indwelling catheter; endocarditis, osteomyelit	q12h i.v.	10–28 days		LNZ, 80.0% vancomycin Microbiological success: 81.8% LNZ, 60.0% vancomycin

Study no.	Study type	Locations	No. of pts (ITT)	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Comparator(s)	Linezolid dose/ duration	Status	Results
								is, meningitis, CNS infections				
EudraCT: 2006-000595-32 [85]	Phase 2, not controlled, OL	Europe	12	<18 years	Central indwelling catheter-related bacteraemia in haemato-oncological pts	Safety and efficacy		New metastatic infections during treatment; lack of response within 7 days of treatment;	None	NA	Completed	NA

Study no.	Study type	Locations	No. of pts (ITT)	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Comparator(s)	Linezolid dose/ duration	Status	Results
								adverse reactions to the drug used				
EudraCT: 2006-002146-10 [86]	Not controlled, phase 2, OL	Europe	12	<18 years	Tunnel/pocket infections (cellulitis) of central indwelling catheters in haemato-oncological pts	Tolerability of antibiotic lock; feasibility of outpatient therapy		New metastatic infections during treatment; lack of response within 7 days of treatm	None	NA	Completed	NA

Study no.	Study type	Locations	No. of pts (ITT)	Age	Type of infection	Primary endpoints	Secondary endpoint	Main exclusion criteria	Comparator(s)	Linezolid dose/ duration	Status	Results
								ent; adverse reactions to the drug used				

pts, patients; ITT, intention to treat; OL, open label; CAP, community-acquired pneumonia; HIV, human immunodeficiency virus; q12h, every 12 h; i.v., intravenous; PO, per os; AE, adverse event; RCT, randomised controlled trial; cSSTI, complicated skin and soft-tissue infection; CoNS, coagulase-negative staphylococci; q6h, every 6 h; DB, double blind; CNS, central nervous system; NA, not available.

Table options

In two previously cited RCTs, linezolid is one of the comparators for ceftaroline [20] and [21].

No PIP is currently available on linezolid.

3.8. Moxifloxacin

Moxifloxacin is a fourth-generation fluoroquinolone with a rapid bactericidal effect [87]. It acts by interfering with topoisomerase II and IV, which are essential enzymes for the replication, transcription and repair of bacterial DNA. Its spectrum of activity covers Gram-positive bacteria (including S. pneumoniae and S. aureus), Gram-negative bacteria, some

anaerobes and atypical strains. Moxifloxacin has high oral availability and rapidly distributes to extravascular spaces, with a strong affinity for alveolar tissue.

Although moxifloxacin displayed a favourable safety profile in clinical trials, the EMA-approved indications have been recently restricted due to the increased risk of adverse hepatic reactions [88]. They include second-line therapy of acute bacterial sinusitis, acute exacerbations of chronic bronchitis (AECB) and CAP. Warnings have also been raised for spontaneous tendon ruptures, worsening of myasthenia gravis symptoms and severe skin reactions. Other serious adverse effects include irreversible peripheral neuropathy and QTc prolongation [89].

The main advantages of moxifloxacin are once-daily administration, fast bactericidal action, good tissue penetration and broad spectrum of activity, including mycobacteria.

Moxifloxacin is not licensed for paediatric use, with the exception of the topical formulation, and its dosage in children is still to be determined. The WHO guidelines on the treatment of drug-resistant tuberculosis recommend a moxifloxacin dose of 7.5–10 mg/kg/day (maximum 400 mg) in children [90]. In the USA, a trial is currently investigating the pharmacokinetics of single-dose moxifloxacin in children aged 3 months to 14 years [91].

Four trials on the systemic use of moxifloxacin (hydrochloride) in children are being conducted in the EU (Table 9).

Table 9.

European clinical trials on moxifloxacin involving paediatric patients.

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint(s)	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Moxifloxacin dose/duration	Status	Results
NCT01069900, EudraCT 2009-015578-37 [66] and [67]	Phase 3, RCT, DB	Europe, Asia, Central and South America, USA	450	3 months to 17 years	IAI	Comparative safety	Evaluation of musculoskeletal AEs; electrocardiogram profiles; clinical response at TOC among subjects with a bacteriologically confirmed complicated IAI;	Spontaneous bacterial peritonitis; pancreatic processes; early acute or suppurative (non-perforated) appendicitis; severe immunosuppression; congenital or	Ertapenem 1 g i.v. OD for a minimum of 3 days (age 13 years to <18 years) or 15 mg/kg body weight i.v. BID not to exceed 1 g daily (age <13 years) If switched to PO: amoxicillin/clavulanic acid PO	12–17 years (≥45 kg): 400 mg i.v. OD for a minimum of 3 days If switched to PO: 400 mg OD <12 years: 4 mg/kg BID	Recruiting	NA

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint(s)	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Moxifloxacin dose/duration	Status	Results
							clinical and bacteriological response to treatment at a ‘during therapy’ visit and at EOT	acquired QT prolongation, concomitant treatment with QT-prolonging drugs; tendon disease/disorder related to quinolone treatment; pathogenic organisms resistant to study	45 mg amoxicillin/kg body weight BID not to exceed 875 mg amoxicillin BID (total treatment duration 5–14 days)	i.v. and PO (maximum 400 mg daily) for 5–14 days		

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint(s)	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Moxifloxacin dose/duration	Status	Results
								drugs; musculoskeletal disease with high risk for arthritis or tendinitis				
NCT00932802[92] and [93]	Phase 4, observational	Europe, Central and South America, Asia,	50000	≥12 years	Outpatients with AECB	Evaluation of impact of AECB on the patient and community; effect and	AEs collection; course of symptom relief; evaluation of frequency of new exacerbations;	According to local product information	None	According to investigator	Completed	No subanalysis for the paediatric cohort

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint(s)	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Moxifloxacin dose/duration	Status	Results
		Africa				safety of moxifloxacin in daily life clinical practice	progression of chronic respiratory disease; speed of return to normal daily life activities					
NCT00997997[94]	Phase 4, observational	Europe, Asia, Africa	6300	≥10 years	cSSTIs	Efficacy (course of severity of infection and of	AEs collection; overall assessment of tolerability by the	According to local product information	None	According to investigator	Completed	No subanalysis for the paediatric

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint(s)	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Moxifloxacin dose/duration	Status	Results
						clinical signs and symptoms, duration until improvement, recovery, wound closure, reuse of moxifloxacin)	physician					cohort

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint(s)	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Moxifloxacin dose/duration	Status	Results
NCT00930488[95]	Observational, phase 4	Europe, Asia, Africa	7241	NA	Acute bacterial sinusitis	Evaluation of potential benefits of antibacterial therapy with moxifloxacin	Evaluation of tolerability and safety of moxifloxacin in daily practice	According to local product information	None	According to investigator	Completed	
EudraCT 2009-017319-13 [96]	RCT	Europe	1300	<18 years	AOM with otorrhoea and tympanosto	Safety and efficacy of topical moxifloxacin; demon	–	Tympanostomy tubes containing antimicrobial agents; current	Placebo	NA	Ongoing in Belgium; prematurely ended in	

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint(s)	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Moxifloxacin dose/duration	Status	Results
					my tubes	stration of the therapeutic superiority of moxifloxacin at EOT		acute or chronic non-tube otorrhoea or otitis externa or malignant otitis externa; ear infection of fungal or mycobacterial origin; herpetic infection; mastoiditis or other suppurati			Denmark and Finland	

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint(s)	Secondary endpoint(s)	Main exclusion criteria	Comparator(s)	Moxifloxacin dose/duration	Status	Results
								ve non-infectious disorders in the ear(s)				

pts, patients; RCT, randomised controlled trial; DB, double blind; IAI, intra-abdominal infection; TOC, test of cure; EOT, end of therapy; i.v., intravenous; OD, once daily; BID, twice daily; PO, per os; AECB, acute exacerbations of chronic bronchitis; AE, adverse event; cSSTI, complicated skin and soft-tissue infection; NA, not available; AOM, acute otitis media.

Table options

A RCT is evaluating the safety and efficacy of moxifloxacin versus ertapenem in hospitalised children with cIAIs. The study is still recruiting participants. The safety endpoints focus on cardiac and musculoskeletal AEs [66] and [67].

The remaining three studies are observational phase 4 trials, but their paediatric relevance is limited as the number of enrolled children is not reported and no paediatric subanalysis is available. The first study enrolled outpatients aged ≥12 years under daily treatment with oral moxifloxacin for AECB. It aimed to determine the impact of AECB on the patient and the community and to evaluate the safety and efficacy of moxifloxacin in daily practice [92] and [93]. The second study evaluated patients aged ≥10 years with cSSTIs: moxifloxacin under daily-life treatment conditions appeared effective and the incidence of AEs was low [94]. The third study evaluated the potential benefits, tolerability and safety of moxifloxacin in patients with acute bacterial sinusitis [95].

Finally, a European trial is currently evaluating the safety and efficacy of topical moxifloxacin otic solution in children with acute otitis media with otorrhoea and tympanostomy tubes [96].

PIPs for treatment of pelvic inflammatory disease in female adolescents aged from 12 years to <18 years and cIAIs aged from 3 months to <18 years have been agreed on moxifloxacin [97], [98], [99] and [100].

3.9. Retapamulin

Retapamulin is a topical antibiotic belonging to the new class of pleuromutilins. It is approved by the EMA for bacterial superficial skin infections, such as impetigo due to meticillin-susceptible S. aureus or Streptococcus pyogenes, in patients ≥9 months of age. Retapamulin inhibits bacterial protein synthesis by interacting at a site on the 50S subunit of the bacterial ribosome through a unique mechanism. Systemic exposure following topical application through intact skin is low. The most common adverse reaction is irritation at the application site [101] and [102].

Retapamulin ointment was superior to placebo in adults and children with primary impetigo (Table 10). Pruritus at the application site was the most common AE (6%) [103] and [104]. Retapamulin and sodium fusidate had comparable clinical and bacteriological efficacy in the treatment of impetigo in adults and children aged ≥9 months; both drugs were well tolerated [105], [106] and [107]. The pharmacokinetics of retapamulin has been evaluated in 86 children (2–24 months) with secondarily infected traumatic lesions, dermatoses or impetigo. The study has been completed but the results have not been published [108] and [109]. A pharmacovigilance study will monitor the prescriptions of retapamulin across the EU in infants <9 months of age [110].

Table 10.

European clinical trials on topical retapamulin involving paediatric patients.

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Retapamulin dose/duration	Status	Results
NCT00133848[103] and [104]	RCT, DB, phase 3	Asia, Europe, Central and South America	210	≥9 months	Primary impetigo	Clinical response at EOT	Clinical response at FU; impetigo lesion area at EOT and FU	Systemic infection; serious or life-threatening underlying diseases	Placebo ointment	1% ointment BID for 5 days	Completed	Success rate: 85.6% retapamulin, 52.1% placebo
NCT00133874, EudraCT 2004-004439-70 [105], [106] and [107]	RCT, SB, phase 3	Canada, South America, Europe, Asia	520	≥9 months	Impetigo	Clinical response (no need for additional antibiotic treatme	Clinical response at FU; microbiological response at	Systemic infection; serious or life-threatening underly	2% sodium fusidate ointment TID	1% ointment BID for 5 days	Completed	Comparable clinical efficacy (PPP: retapamulin 99.1%

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Retapamulin dose/duration	Status	Results
		, South Africa				nt) at EOT	EOT and FU; extent of impetigo lesion area at EOT and FU	ing disease	for 7 days			vs. comparator 94.0%; ITT population: 94.8% retapamulin vs. 90.1% comparator). Similar bacteriological efficacy

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Retapamulin dose/duration	Status	Results
NCT00555061, EudraCT 2006-003374-10 [108] and [109]	Non-randomised, OL, phase 4	South America, Europe, Central America, South Africa, USA	87 (1 pt did not receive study medication)	2–24 months	Secondarily infected traumatic lesions and dermatoses; impetigo	Pharmacokinetics of retapamulin	Age-stratified clinical success at FU; bacteriological response at FU by baseline pathogen; safety of retapamulin	Hypersensitivity to pleuromutilin or components of the ointment; prematurity; animal/human bites, puncture wounds or abscesses;	None	1% ointment BID for 5 days	Completed	NA

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Retapamulin dose/duration	Status	Results
								chronic ulcerative lesions; systemic infection; need for surgical intervention; prior systemic antibiotics; systemic corticosteroid				

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Main exclusion criteria	Comparator	Retapamulin dose/duration	Status	Results
								treatment				
NCT01153828[110]	Observational, pharmacovigilance study	Europe	NA	Any	Impetigo, secondarily infected traumatic lesions	Age-stratified monitoring of prescribed use of retapamulin	Co-prescription of retapamulin and topical mupirocin; co-prescription of retapamulin and topical fusidic acid	Enrolment in the General Practice Research Database of <1 month duration	None	NA	Ongoing, but not recruiting	NA

pts, patients; RCT, randomised controlled trial; DB, double blind; EOT, end of treatment; FU, follow-up; BID, twice daily; SB, single blind; TID, three times daily; PPP, per-protocol population; ITT, intention-to-treat, OL, open label; NA, not available.

Table options

No PIP is available on retapamulin.

3.10. Telithromycin

Telithromycin is a semisynthetic erythromycin derivative and the first member of the ketolides. It was approved in Europe in 2001 and in the USA in 2004. It acts through inhibition of bacterial protein synthesis through binding to the bacterial ribosome with higher affinity than erythromycin [111] and [112]. Following oral administration, telithromycin is rapidly absorbed and diffused into tissues and phagocytes. Telithromycin is used to treat respiratory infections as it is effective against macrolide-resistant S. pneumoniae [113]. In Europe it is marketed for the treatment of adults with mild-to-moderate CAP, AECB, acute sinusitis and tonsillitis/pharyngitis caused by Group A β-haemolytic streptococci (GAS). It is also licensed at 25 mg/kg once daily in children aged 12–18 years with GAS tonsillitis/pharyngitis when β-lactams are not appropriate [114].

The most common side effects are gastrointestinal symptoms. Prolonged QTc intervals may also be observed. Recently, serious safety concerns have been raised regarding risks for severe liver toxicity, visual disturbances, transient loss of consciousness and exacerbations of myasthenia gravis: indeed, part of the telithromycin molecule acts as an antagonist of cholinergic receptors of muscles, eye and liver. For safety reasons, in 2007 the FDA revised the labelling removing two indications (acute bacterial sinusitis and AECB), whilst the EMA has recommended to restrict the use of telithromycin to the treatment of bronchitis, sinusitis and tonsillitis/pharyngitis caused by bacterial strains that are resistant to or cannot be treated with β-lactams or macrolides [115] and [116]. Following the benefit/risk evaluation by the CHMP, the marketing authorisation holder decided to stop the paediatric development programme [117]. Therefore, three studies investigating infants and children with acute otitis media were terminated in Europe (Table 11) and no PIP has been issued [118], [119] and [120].

Table 11.

European clinical trials on telithromycin involving paediatric patients.

Study no.	Study type	Locations	No. of pts,	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Exclusion criteria	Comparator(s)	Telithromycin dose/duration	Comments
NCT00174811[118]	RCT, DB, phase 3	South America, Europe, Asia, USA	639	6–59 months	AOM	Clinical cure at EOT and TOC visit	Time to symptom resolution; clinical cure by causative pathogen; bacteriological eradication at comparative safety; PK substudy; health resource utilisation and impact on usual activities	Uncertain AOM not needing antibiotics; otorrhoea or tympanostomy tubes; congenital abnormalities; congenital prolonged QT syndrome, treatment with agents interfering with QT prolongation; uncorrected hypokalae	Cefuroxime 15 mg/kg BID for 10 days (PO)	25 mg/kg OD for 5–10 days (PO)	Study was terminated before enrolment was completed (no definite conclusions on efficacy available). Cure rate: telithromycin 90.0%, cefuroxime 92.7%

Study no.	Study type	Locations	No. of pts,	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Exclusion criteria	Comparator(s)	Telithromycin dose/duration	Comments
								mia, hypomagnesaemia, bradycardia; myasthenia gravis; known impaired renal function			
NCT00315003[119]	RCT, DB, phase 3	South America, Europe, Israel, USA	321	6 months to 6 years	Suppurative AOM	Time to symptom resolution and clinical cure at the TOC visit	Safety	Mild-to-moderate symptoms and signs of AOM; otorrhoea or tympanostomy tube; congenital long QT syndrome;	Azithromycin oral suspension 10 mg/kg OD on Day 1, followed by 5 mg/kg OD on	25 mg/kg OD for 5 days (PO)	Because of early termination of the study and limited data, no definite efficacy conclusi

Study no.	Study type	Locations	No. of pts,	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Exclusion criteria	Comparator(s)	Telithromycin dose/duration	Comments
								known or suspected uncorrected hypokalaemia, hypomagnesaemia, bradycardia; myasthenia gravis; known impaired renal function; congenital abnormalities; immunodeficiency; hypersensitivity to macrolides	Days 2–5, max. 500 mg on Day 1 and 250 mg/day from Days 2–5		ons can be drawn. Clinical cure rate: telithromycin 78.5%, azithromycin 82.7%. Median time to symptom resolution (ITT population): 3.0 days telithromycin;

Study no.	Study type	Locations	No. of pts,	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Exclusion criteria	Comparator(s)	Telithromycin dose/duration	Comments
											2.75 days azithromycin
EudraCT: 2004-000738-34 [120]	RCT, DB	Europe and non-EU states	900	6–59 months	AOM	Non-inferiority of telithromycin vs. cefuroxime axetil	Comparative efficacy; safety of telithromycin; prevalence of nasopharyngeal carriage of Streptococcus pneumoniae; plasma telithromycin concentrat	Otorrhoea or tympanostomy tube; otitis externa; chronic diseases; congenital prolonged QT syndrome; myasthenia gravis; impaired renal function, hypokalaemia,	Cefuroxime axetil 15 mg/kg BID for 10 days	25 mg/kg OD for 5–10 days	Prematurely ended

Study no.	Study type	Locations	No. of pts,	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Exclusion criteria	Comparator(s)	Telithromycin dose/duration	Comments
							ions in a subset of subjects; health resource utilisation and impact on usual activities of parents/legally authorised representatives	hypomagnesaemia, bradycardia			

pts, patients; RCT, randomised controlled trial; DB, double blind; AOM, acute otitis media; EOT, end of treatment; TOC, test of cure; PK, pharmacokinetic; BID, twice daily; PO, per os; OD, once daily; ITT, intention-to-treat; EU, European Union.

Table options

3.11. Tigecycline

Tigecycline is the first member of the glycylcyclines. It is structurally similar to tetracyclines and acts as a protein synthesis inhibitor by binding to the 30S ribosomal subunit of bacteria [121] and [122]. Its bacteriostatic activity is maintained in the presence of several resistance mechanisms that affect other antibiotics and it covers a variety of Gram-positive and Gram-negative bacteria (including MRSA, S. maltophilia, A. baumannii and multidrug-resistant Enterobacteriaceae), anaerobes and atypical bacteria. It is not active against P. aeruginosa, Morganella or Providencia spp.[121] and [122].

Tigecycline was given a fast-track approval by the FDA for the treatment of cSSTIs, cIAIs and CAP. It was authorised in the EU in 2006 for adults with cSSTIs (excluding diabetic foot infections) and cIAIs; a variation application to include CAP in licensed indications was withdrawn in 2008.

Tigecycline has similar side effects to the tetracyclines, such as diarrhoea, nausea and vomiting. It may also cause photosensitivity, pseudotumour cerebri and pancreatitis [121], [122] and [123]. Its use is to be avoided in young children and during pregnancy owing to its effects on teeth and bone. Recently, a warning regarding increased mortality risk associated with tigecycline use has been issued [124] and [125]. A recent meta-analysis of RCTs of tigecycline documented that septic shock and superinfections were significantly more frequent in patients treated with tigecycline than with comparators. The CHMP has recommended to restrict tigecycline use to only when other suitable alternatives are not available and to include new warnings to inform prescribers of the higher mortality recorded in tigecycline trials [126].

Two paediatric studies on tigecycline have been conducted in Europe (Table 12). A multicentre study investigated emergency use of the drug in adults and children aged ≥8 years infected by resistant bacteria where other treatments had not been successful. The study has been completed but results for the paediatric cohort are not available [127]. A phase 2 study evaluated the PK profile of multiple doses of tigecycline in children aged 8–11 years with cIAIs, cSSTIs or CAP to identify an appropriate dose regimen (0.75, 1 or 1.25 mg/kg q12h) and to assess the safety profile and efficacy of tigecycline [128] and [129]. The ca. 1.2 mg/kg q12h dosage appeared the most appropriate, to be tested in phase 3 clinical trials. In this cohort, nausea was the most frequent AE and the overall clinical cure rate was 94%.

Table 12.

European clinical trials on tigecycline involving paediatric patients.

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Exclusion criteria	Comparator	Tigecycline dose/duration	Results
NCT00205816[127]	Non-randomised, uncontrolled, OL, phase 3	Europe, USA	27	≥8 years	Bacterial infections due to resistant pathogens	Mechanism for the emergency use of tigecycline in clinical situations	Safety and efficacy	Expected survival <2 weeks; hypersensitivity to tigecycline, tetracyclines or related compounds; pregnancy or breastfeeding	None	Tigecycline, 100 mg i.v. followed by 50 mg q12h or q24h for 5–90 days	NA for the paediatric cohort
NCT00488345[128] and [129]	Randomised, OL, phase 2	Europe, South Africa,	59	8–11 years	cIAI, cSSTI, CAP	PK properties of ascending doses	Population PK model, safety,	Endocarditis; artificial heart valve or infected device; hypersensit	NA	Tigecycline 0.75, 1 or 1.25 mg/kg	Mean PK values: Cmax, 1899 ng/mL; Tmax, 0.56 h; between-

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Exclusion criteria	Comparator	Tigecycline dose/duration	Results
		Asia, USA					efficacy	ivity to tigecycline or other related compounds; immunosuppressed patients; serious infections (e.g. necrotising fasciitis, gangrene, empyema, abscess, etc.); critical conditions (sepsis and septic shock)		i.v. for ≥5 days	dose AUC, 2833 ng h/mL; weight-normalised clearance, 0.503 L/h/kg; and Vd,ss, 4.88 L/kg. Overall clinical cure rates at TOC: 94%, 76% and 75% in the 0.75, 1 and 1.25 mg/kg cohorts, respectively. Nausea in

Study no.	Study type	Locations	No. of pts	Age	Type of infection	Primary endpoint	Secondary endpoint(s)	Exclusion criteria	Comparator	Tigecycline dose/duration	Results
											50% of patients. PD simulations predicted that a dosage of ca. 1.2 mg/kg q12h would lead to therapeutic target attainment levels of up to 82% for the target AUC0–24/MIC ratios

pts, patients; OL, open label; i.v., intravenous; q12h, every 12 h; q24h, every 24 h; NA, not available; cIAI, complicated intra-abdominal infection; cSSTI, complicated skin and soft-tissue infection; CAP, community-acquired pneumonia; PK, pharmacokinetic; Cmax, peak concentration of drug; Tmax, time at which Cmax is observed; AUC, area under the

concentration–time curve; Vd,ss, volume of distribution at steady state; TOC, test of cure; PD, pharmacodynamic; MIC, minimum inhibitory concentration.

Table options

A PIP has been agreed for treatment of cSSTIs and cIAIs in children aged 8–18 years [130].

4. Discussion

The increasing problem of multidrug-resistant bacteria will encourage the development and hopefully subsequent approval of new antibiotics [2]. The need for targeted studies on antibiotics in children has been recognised as a matter of concern by the regulatory authorities. However, despite the recent efforts in implementing paediatric trials, the number of studies that have been or are being conducted in children in this area still remains strikingly low, especially in Europe. For all the different possible indications for the 11 antibiotics newly approved by the EMA (of which only 2 have paediatric labelling), 31 clinical trials enrolling children in Europe were identified. However, many of these trials were mainly focused on adults and did not provide a subset analysis for the older children recruited, limiting the relevance of their findings. Some studies have been prematurely terminated and others are active but are still not yet recruiting patients. Among paediatric-targeted studies, 18 evaluate the safety and efficacy of new compounds, 4 are PK studies, but only 2 focus on neonates, the population in which dosing is likely most different from adults or older children. We could identify only one paediatric pharmacovigilance study on antibiotics in Europe. Nearly all studies with an agreed PIP have just started or are not yet recruiting. To our knowledge, this is the first comprehensive review on clinical trials conducted in the EU on antibiotics in children. Previous reports in the USA have documented an increase in the quantity and quality of paediatric controlled trials, demonstrating a success of the FDA paediatric exclusivity programme. However, it also emerged that dissemination of trial results in the literature is limited, as barely one-half of studies were published and determined labelling changes [131], [132] and [133]. A possible bias should also be taken into account in our study: unregistered trials, as well as unpublished data retained by pharmaceutical companies, may have led to an underestimation of available results. The new interventions and legislation introduced both in the USA and Europe should further promote drug evaluation in paediatrics, but the efficacy of these processes is under review. There are a number of steps that would improve the design of new antibiotic trials in children in Europe. These include an adequate knowledge of the basic epidemiology of key clinical syndromes in children (CAP, SSTI, IAI, etc.) through prospective observational studies. Second, a closer collaboration between clinicians and the pharmaceutical industry is necessary, particularly in early study design. The EMA has created a European paediatric network of research networks, investigators and

centres with expertise in paediatric clinical studies [European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)], that supports high-quality studies in children and helps with fostering closer links between industry, the regulators, patient representatives and academic clinical trial networks [134].

The EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA) have launched a public–private partnership called the Innovative Medicines Initiative (IMI), aimed at improving and speeding up the drug development process. Combating and treatment of infectious diseases is a key research priority of the IMI programme: in May 2012, the IMI launched its 6th Call on the theme ‘Combating Antibiotic Resistance’ that includes ‘innovative trial design & clinical drug development’ [135]. It was perhaps slightly disappointing that the call did not include any specific development programme for children, with the call being only on clinical trials for adults. One potential model could be based on the Paediatric European Network for Treatment of AIDS (PENTA), established in 1991 as a collaboration between paediatric human immunodeficiency virus (HIV) centres in Europe, working closely with industry and the regulator to rapidly develop appropriate studies in children in parallel with adult HIV drug development programmes [136]. These studies are often a combination of PK, safety and strategic trials, rather than expensive and often not appropriate large phase 3 efficacy studies. PENTA has now become PENTA-ID, and can work with Pharma to develop new antimicrobials in Europe. This structured approach may actually speed drug development within the current regulatory framework. This level of collaboration with baseline observational studies, linked to planned interventional studies, is now required for antibiotics under early development.

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