Extrapolation in antibacterial agents

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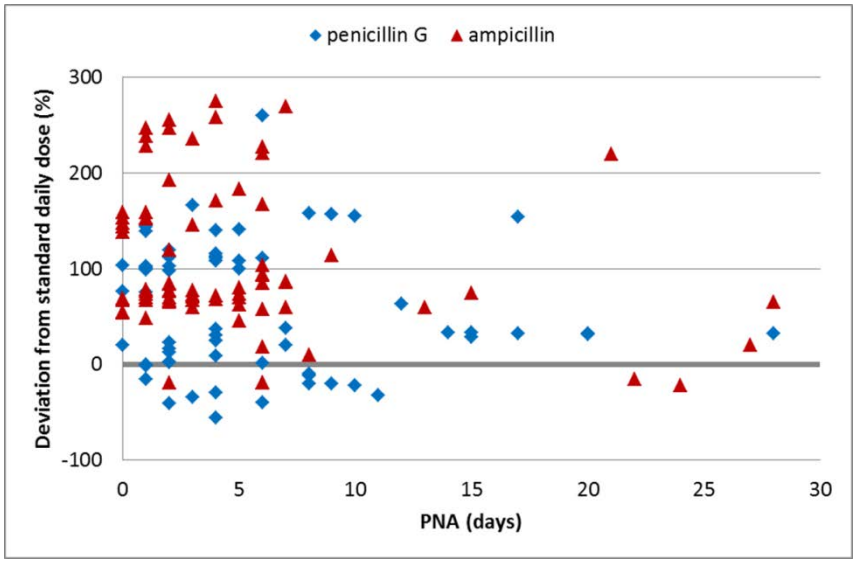
EMA meeting, 30.09.2015

Glossary

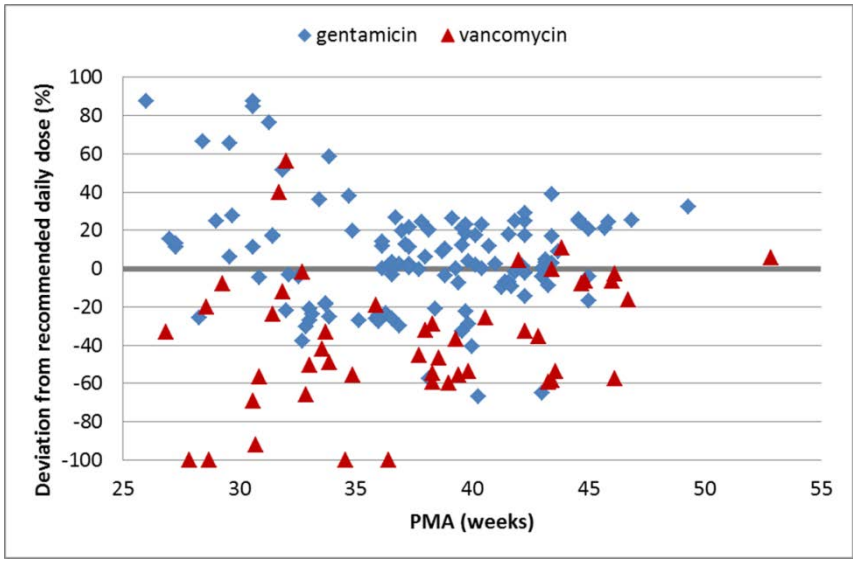
- PIP: Paediatric Investigation Plan
- AHOM: acute haematogenous osteomyelitis
- CAP: community-acquired pneumonia
- cIAI: complicated intra-abdominal infections
- cSSTI: complicated skin and soft tissue infections (currently: acute bacterial skin and skin strcuture infections, aBSSSIs)
- cUTI: complicated urinary tract infections
- NP: nosocomial pneumonia
- PID: pelvic inflammatory disease
- VAP: ventilator-associated pneumonia
- MCS: Monte Carlo simulation
- LOS – late onset sepsis

Deviations in dosing of antibiotics in neonates: ESNEE data (89 EU NICUs)

Penicillin and ampicillin



Vancomycin and gentamicin



If well-tolerated – doses are in general higher than recommended
If toxicity – doses are in general lower than recommended

Reference: Blue Book

Metsvaht *et al*. BMC Pediatr. 2015 Apr 16;15:41

PIPs of antibacterial agents

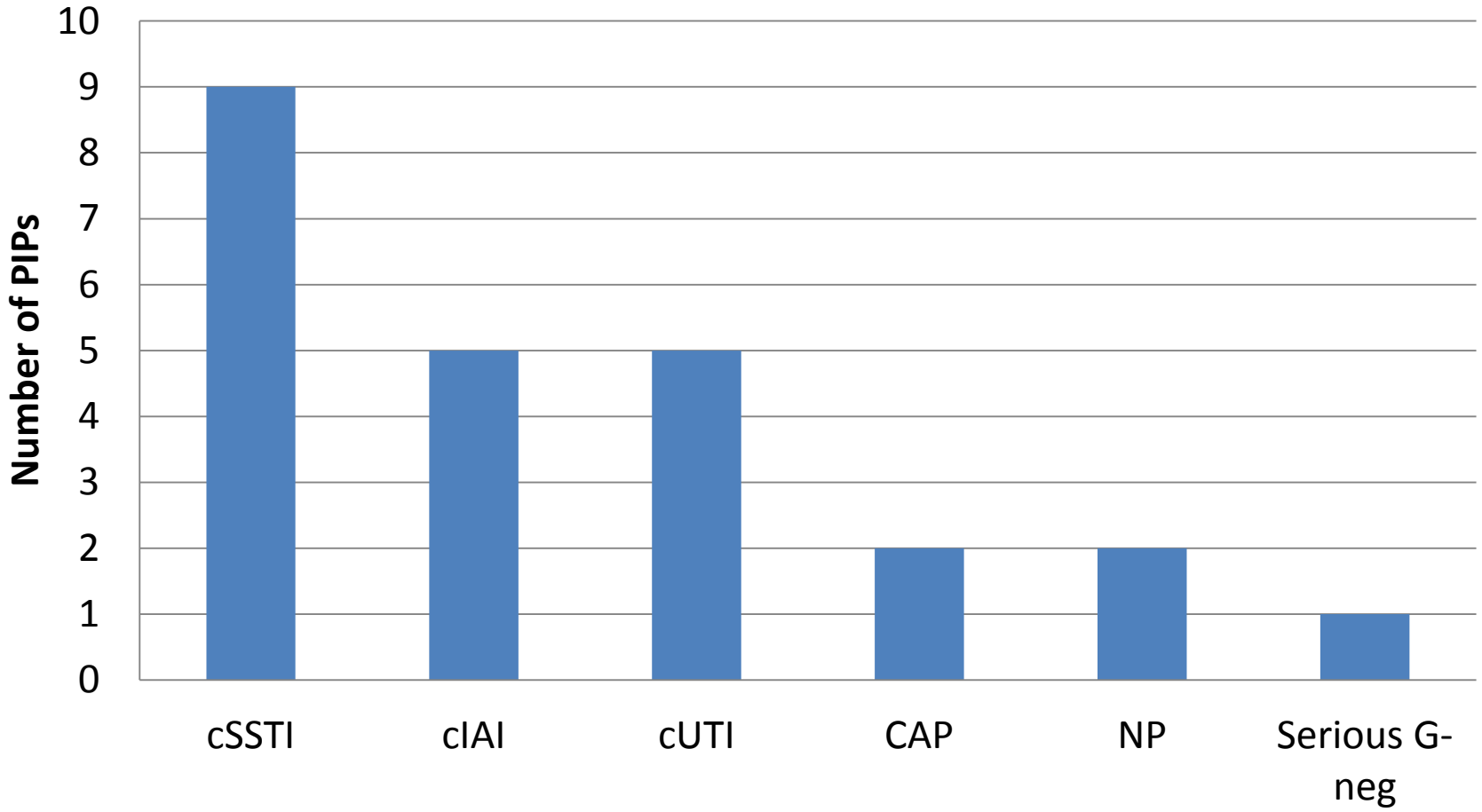
- 16 agreed PIPs (with EMA Decisions)
  - excluding antibacterial agents for topical use, for inhalation (e.g. cystic fibrosis), for *C difficile*-associated diarrhoea, and for eradication of *H pylori*
- Full waiver granted for delafloxacin for the treatment of cSSTI
  - New PIP expected for CAP (if this indication is pursued in adults)
- 4 PIPs withdrawn
- 2 currently under review

EMA Decisions on antibiotic PIPs (n = 16)

Active substance	PIP number	Indications covered	Waiver
Ceftaroline fosamil	769	cSSTI, CAP	No
Ceftobiprole medocaril	205	cSSTI	No
Ceftazidime/Avibactam	1313	cIAI, cUTI, NP, serious G^-	No
Ceftolozane/Tazobactam	1142	cIAI, cUTI	No
Ceftriaxone/Sulbactam	1568	Extrapolation all adult indications, PK neonates	No
Doripenem	15	cIAI, cUTI, NP	No
Meropenem	898	Sepsis, Meningitis (bacterial)	Above 3 mo
Tigecycline	120	cIAI, CSSTI	Under 8 years
Eravacycline	1555	cSSSTI, cUTI	Under 8 years
Telavancin	239	cSSTI, HAP	No
Dalbavancin	16	cSSTI	No
Oritavancin	1270	cSSTI	No
Vancomycin	1311	Late-onset sepsis	Above 3 mo
Solithomycin	1581	Gonococcal disease, CAP	No*
Moxifloxacin	288	PID, cIAI	Yes*
Tedizolid	1379	cSSTI	No

*PID: only in adolescent females; gonococcal disease: only in adolescents

Indications covered in agreed PIPs



OTHER: Gonococcal disease: adolescents; PID, LOS, BM, chronic OM, bone&joint infection, bacterial sepsis, perioperative infections

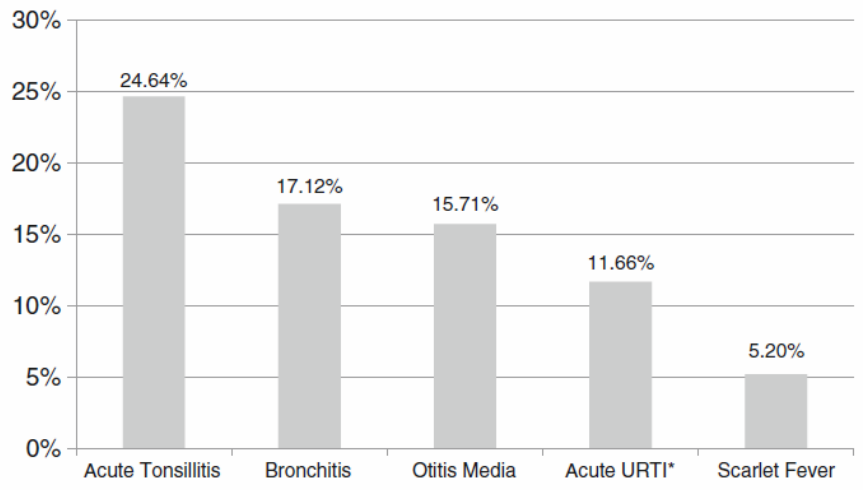
Indications for antibiotic use in paediatrics

AB use in 32 EU paediatric hospitals

Characteristics	*n*	%	*n*	%
	treatment		prophylaxis	
respiratory	127	29	42	24
systemic	67	15	13	7
ear, nose, throat	60	14	10	5
gastrointestinal	48	11	31	18
urology	41	9	16	9
SSTI&bone	35	8	9	5
CNS	22	5	8	4
undefined	17	4	34	19
eye	6	1	1	1
CVC	5	1.2	5	2
gynaecology	1	0.2	2	1

J Antimicrob Chemother. 2010 Oct;65(10):2247-52
Eur J Pediatr. 2013 Jun;172(6):787-95

AB use in outpatient in Germany



Indications in which antibiotics are studied are not the most common in paediatrics

Pathogen and Antibiotic Class	EARS-Net	ARPEC
Gram-negative pathogens		
Escherichia coli		
Aminopenicillins*	57.2%	67.9% (62.6–73.1)
Third generation cephalosporins	11.9%	12.9% (9.3–16.5)
Aminoglycosides*	11.3%	14.6% (10.9–18.4)
Fluoroquinolones*	23.0%	13.4% (9.8–17.0)
Carbapenems*	0.1%	0.6% (0.07–2.1)
Klebsiella pneumoniae		
Third generation cephalosporins	31.6%	32.5% (25.5–40.2)
Aminoglycosides	27.6%	31.8% (24.8–39.3)
Fluoroquinolones*	30.7%	17.9% (12.4–24.5)
Carbapenems*	13.5%	6.5% (3.3–11.4)
Pseudomonas aeruginosa		
Piperacillin (± tazobactam)*	17.6%	36.0% (27.1–45.7)
Ceftazidime*	14.8%	25.8% (18.5–34.3)
Aminoglycosides*	19.3%	27.3% (19.8–35.9)
Fluoroquinolones	23.1%	23.4% (16.4–31.7)
Carbapenems*	20.5%	32.8% (24.7–41.8)
Gram-positive pathogens		
Staphylococcus aureus		
Methicillin resistance	21.2%	16.4% (12.7–20.8)
Streptococcus pneumoniae		
Penicillin nonsusceptibility	10.8%	13.4% (7.9–20.9)
Macrolide nonsusceptibility*	15.3%	33.1% (24.8–42.2)
Enterococcus faecalis		
High level gentamicin	30.5%	29.5% (21.0–39.2)
Enterococcus faecium		
Vancomycin	8.3%	9.0% (3.7–17.6)

For ARPEC, the proportion of resistant isolates is shown with the 95% confidence interval.

*Difference between EARS-Net and ARPEC resistance percentages is statistically significant ($P < 0.05$).

AB resistance is similar in children and in adults among Gram-positives but differs among Gram negatives

EARS-Net – adults
ARPEC - children

Pediatr Infect Dis J. 2015 Jul;34(7):734-41

Extrapolation of efficacy

Concept Paper on extrapolation of efficacy and safety in medicine development (EMA/129698/2012)

The primary rationale for extrapolation is to **avoid unnecessary studies** in the target population for ethical reasons, for efficiency, and **to allocate resources to areas where studies are the most needed**.

Alternatively, in situations where the **feasibility of studies is restricted**, extrapolation principles may be applied for rational interpretation of the limited evidence in the target population in the context of data from other sources

Possibilities for extrapolation

- **Extrapolation efficacy from studies conducted in adults**
  - Adult drug exposure = paediatric drug exposure
- **PK/PD-based extrapolation**
  - PTA modelled in paediatric patients

Extrapolation efficacy from studies conducted in adults

- **Assumptions**
  - Infecting organisms in adults and children are the same
  - Disease process in adults and children is the same
- **Extrapolation**
  - PK studies should be conducted
  - Efficacy will be extrapolated from adult studies provided that the exposure is the same (AUC)
  - Safety studies should be conducted
    - Is the safety in children different of that in adults?
- **Problem**
  - Paediatric and adult indications for antibiotic use are different

PK/PD based extrapolation: PTA modelled in paedaitric patients

- **Assumption**
  - Infecting organisms and their susceptibility are different
  - Disease process is different

- **Extrapolation studies**
  - PK studies in target population
  - MCS using the most likely microorganism with the highest susceptible MIC value and maximal PD index
  - T>MIC 100% + MIC of intermediately resistant microorganims (+ CNS infection)

- **Problem**
  - Do all patients need so high doses?
  - Safety is of concern and should be tested

Pip/tazo dosing in neonates

Regimen	GA (wks)	PMA (wks)	PNA (days)	Dose (mg/kg)	Dose interval (h)	Infusion (h)	
Neofax		≤29	0–28	100	12	0.5	200mg
		≤29	>28	100	8	0.5	
		30–36	0–14	100	12	0.5	
		30–36	>14	100	8	0.5	
		37–44	0–7	100	12	0.5	200mg
		37–44	>7	100	8	0.5	
		>45	(All)	100	8	0.5	
Harriet Lane	≤36		≤7	75	12	0.5	
	>36		≤7	75	8	0.5	
	≤36		>7	75	8	0.5	
	>36		>7	75	6	0.5	
PMA-based (extended infusion)		≤30		100	8	4	
		30–35		80	6	3	
		35–49		80	4	2	
PMA-based (short infusion)		≤30		100	8	0.5	300mg
		30–35		80	6	0.5	
		35–49		80	4	0.5	480 mg

Antimicrob Agents Chemother. 2014 May;58(5):2856-65

Exceptions in children – extrapolation may not be possible

- CAP – 15% of cases caused by bacteria or virus+bacteria, remaining by viruses (N Engl J Med 2015;372:835-845)
- VAP – mostly caused by *S.aureus*, *P.aeruginosa* is very rare
- AOM – is not an adult disease
- GABHS tonisilitis – efficacy in children worse than in adults
- Neonates –
  - mainly infection without source (neonatal sepsis)
  - are immunotolerant and require higher AB exposure than adults

PK/PD based extrapolation or extrapolation of efficacy is not feasible

Types of clinical development in agreed PIPs

- Site-specific indications (cSSTi, cIAI, cUTI, NP) and similar epidemiology in both populations:
  - Extrapolation of efficacy from adults plus PK (dosing recommendations) and safety study(ies) with descriptive efficacy
  - If feasibility issues: consider need/feasibility for specific PK study plus full extrapolation of efficacy (provided safety data are available from studies in other indications): Ceftazidime/Avibactam (CAZ/AVI) for nosocomial pneumonia caused by Gram$^-$ microorganisms
  - CAP: same approach as for other site-specific indications;
    - however, epidemiology of the disease is different in the paediatric population
    - CAP is not a rare disease
- Indications specific of children (e.g., AOM, GABHS tonsillitis, CAP?): PK (dosing recommendations) plus efficacy/safety study
- Indication in adults based on a limited clinical program, e.g.,
  - Serious Gram negative infections with limited therapeutic options (CAZ/AVI)

Note! No fully powered efficacy studies

No paediatric specific indications – AOM, GABHS tonsillitis

Neonates: Bacterial infections

- **Mostly neonatal sepsis (about 50% of cases)**
  - < 1500 g of all hospitalised babies
    - EOS – 1,5% - 2%
    - LOS – 21% - 25%
  - In patients with risk factors
    - EOS – 4,9%
    - LOS – 26%
- **Other infections**
  - Pneumonia — 7-32% of HAI
  - UTI — 29% device related and 77% of unrelated
  - Meningitis – — 3% of all infections
  - Osteomyelitis – — 1.5% of all infections
  - Endocarditis – — 5-12/100,000 newborns
  - cSSTI — ???

Early Human Development 88S2; 2012: S69–S74
Acta Paediatr. 2010; 99: 665-72
BMC Infect Dis. 2015; 15: 152

Neonatal studies and PIPs

- **Objective:** PK and safety study in neonates (from birth to less than 3 months of age) in patients with LOS
  - 13/16 agreed PIPs either as a single study or as separate studies
  - Single or multiple dose PK study (depending on the agent) and safety study
  - Add-on/combination studies (need to cover meningitis) given the immaturity of their immunological system, particularly in preterm neonates
  - No waiver except tetracyclines and quinolones
- In neonates undergoing lumbar puncture for clinical care measurement of the antibacterial agent in CSF is encouraged

Issues for discussion: general (1)

- Which is best methods for extrapolation – adult drug exposure or paediatric PTA?
  - Paediatric PTA – higher doses and exposure than in adults
- Do we need determination of antibiotic concentrations at the site of the infection? (e.g., epithelial lining fluid, cerebrospinal fluid etc.) or can we extrapolate?
- Are the PK characteristics dependent on the indication?
  - In adults dosing is first defined in healthy subjects

Issues for discussion (2)

- **Site-specific indications:**
  - CAP: epidemiology very different from that in adults. Can we extrapolate?
  - NP/VAP: disease is rare, the underlying conditions are different, infecting organisms are different– can we extrapolate efficacy from adults and safety from other indications
- **Paediatric development in case of a limited clinical program in adults (serious infections with resistant organisms)**
  - on a case-by-case basis BUT
    - no need to enrich paediatric studies with multidrug-resistant microorganisms
    - assumption is that PK would be the same and that safety can be extrapolated for a standard study performed in a site-specific indication

Issues for discussion: neonates (2)

- Estimation of first dose: allometric scaling + maturation function OR physiologically-based PK modelling OR both?
  - Is delay in neonatal studies needed/justified?
- Disease is specific, disease process and outcome of the therapy are unlikely or unknown to be comparable between adults and children
- Is there a need for a higher PK/PD index (AUC/MIC, T>MIC) than in immunocompetent adults?
- Is there a need for higher dose due to potential risk of meningitis

Issues for discussions (4)

- **Immunocompromised patients:**
  - Data on bacterial eradication usually available in animal models of infection (e.g., murine thigh-infection model in immunosuppressed rats)
  - Efficacy results not always available in immunocompromised adults
  - Is there a need for a higher PK/PD index (AUC/MIC, T>MIC) than in immunocompetent adults?
- **Cystic fibrosis**
  - No indication in adults but PK is different and antibiotics are needed
- **How to deal with uncertainties in the RMP**
  - Paediatric indication based on full extrapolation (e.g., NP caused by Gram-negative microorganisms)
  - Extrapolation of safety across indications (e.g. from cIAI to NP)