Antibiotics in Focus
New Drugs for Old Bugs

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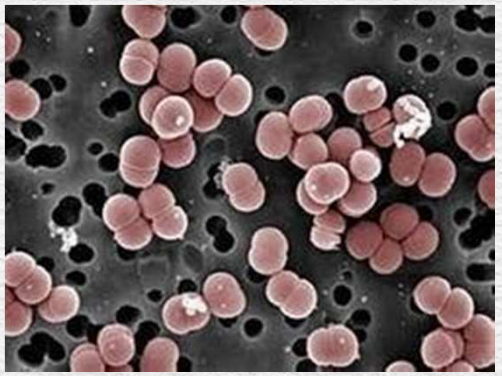
23rd Annual Convention
Pediatric Infectious Disease Society of the Philippines
February 19, 2016

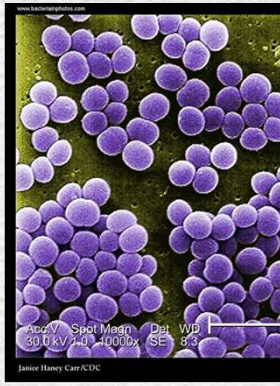
Objectives

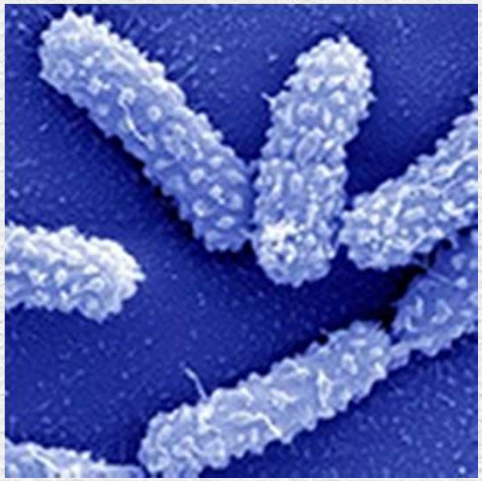
- To discuss the theoretical uses of new antibiotics for various paediatric infections
- To specify what are the off-label drugs for children
- To indicate the new antibiotics that are locally available

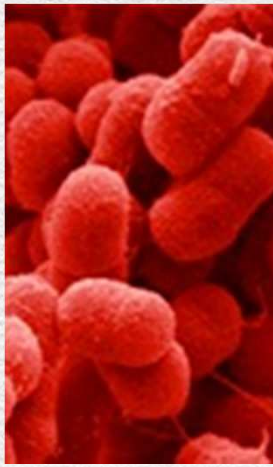
“ESKAPE” Pathogens

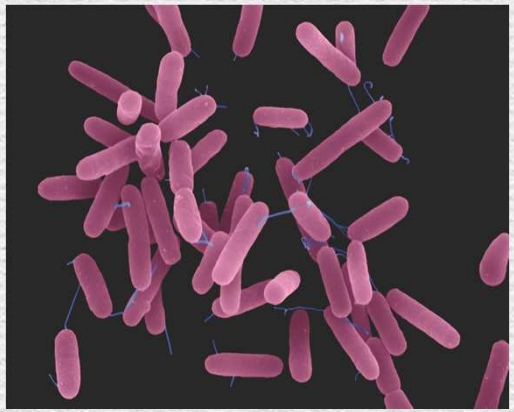
- ***Enterococcus faecium***
- ***Staphylococcus aureus***
- ***Klebsiella pneumoniae***
- ***Acinetobacter baumanii***
- ***Pseudomonas aeruginosa***
- ***Enterobacteriaceae***

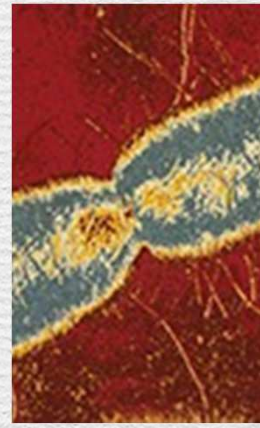












d Bugs, Bad Bugs

lultidrug-resistant bacteria (MDR)

resistant to one or more antibiotics belonging to 3
r more antimicrobial classes

xtensively drug-resistant bacteria (XDR)

resistant to all antibiotics except colistin

an-drug-resistant bacteria (PDR)

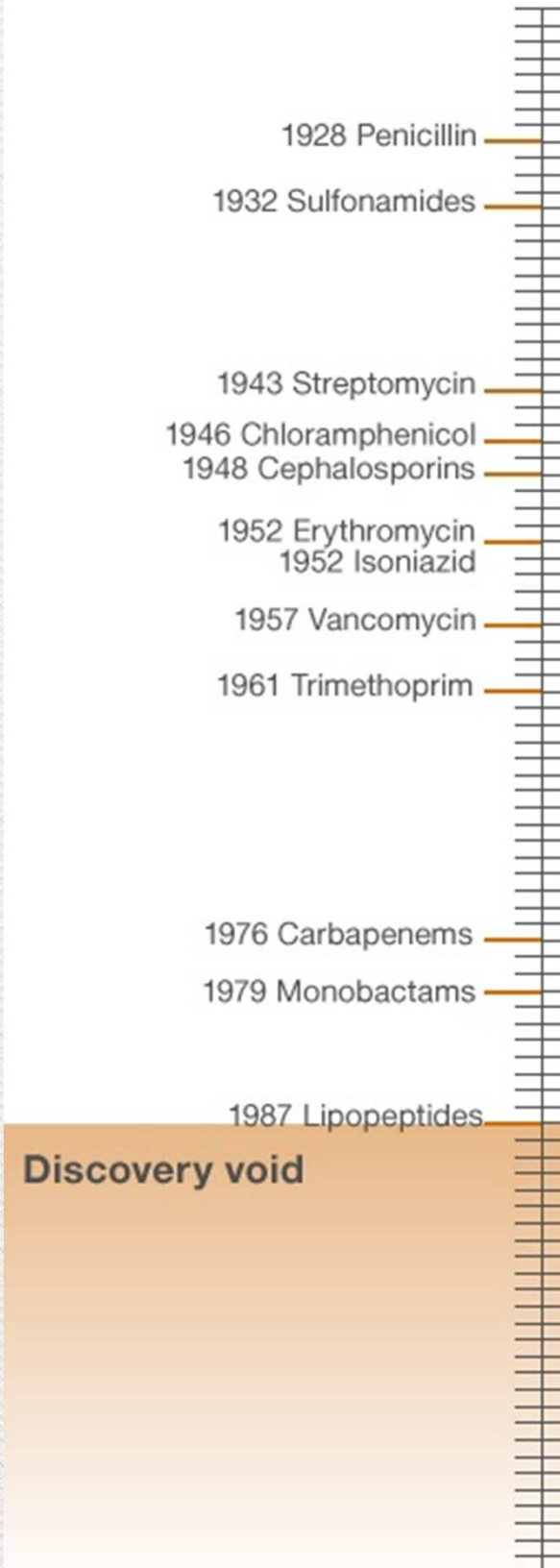
resistant to all available antibiotics, including colis

‘Innovation Gap”

lo new class of antibiotics to
reat systemic bacterial
nfections has been
iscovered since 1987

0 x ’20 Initiative of IDSA

DA set up the FDA Safety
nd Innovaton Act to try to
ncourage research into new
ntibacterials



"The10 x ’20 Initiative

A proGram initiated by the Infectious Diseases Society of America (IDSA) in 2010

Aim: To develop **ten** new safe and effective antibacterial drugs by **2020**

Main targets: ESKAPE pathogens

Boucher HW et al. 10 x ’20 Progress- Development of New Drugs active agai
Gram-negative bacilli: An Update from the Infectious Disease Society of Amer
Clin Infec Dis 2013;56 (12):1685-94.

Antibacterial	Year Approved	Novel Mechanism?
Rifapentine[b]	1998	No
Quinupristin/dalfopristin[c]	1999	No
Moxifloxacin	1999	No
Gatifloxacin[d]	1999	No
Linezolid	2000	Yes
Cefditoren pivoxil	2001	No
Ertapenem	2001	No
Gemifloxacin[d]	2003	No
Daptomycin	2003	Yes
Telithromycin[d]	2004	No
Tigecycline[e]	2005	Yes
Doripenem	2007	No
Telavancin	2009	Yes
Ceftaroline fosamil	2010	No

[a] Rifaxamin (Food and Drug Administration [FDA] approved in 2004) and fidaxomicin (FDA approved in 2011) are not systemically absorbed, and so are not included on this list.

[b] Antituberculous agent.

[c] Infrequently used due to adverse event profile.

[d] Withdrawn from market due to adverse event profile.

[e] Label warning regarding possible excess mortality.

Systemic Antibacterial Drug Approvals since 2000

TIBACTERIAL DRUG	YEAR APPROVED	ANTIBIOTIC CLASS	LOCALI AVAILAB
Linezolid	2000	Oxazolidinone	Yes
Ertapenem	2001	Carbapenem	Yes
Daptomycin	2003	Lipopeptide	Yes
Tigecycline	2005	Glycylcycline	Yes
Doripenem	2007	Carbapenem	Yes
Telavancin	2009	Glycopeptide	No
aroline fosamil	2010	Cephalosporin	No

Recent FDA Antibiotic Approvals

NTIBACTERIAL DRUG	YEAR APPROVED	ANTIBIOTIC CLASS
Dalbavancin	May 2014	Glycopeptide
Oritavancin	August 2014	Glycopeptide
Tedizolid	2014	Oxazolidinone
Ceftobiprole	2014	Cephalosporin
Ceftolozane-tazobactam	December 2014	Cephalosporin-β-lactamase inhibit combination
Ceftazidime-	February 2015	Cephalosporin-β-lactamase inhibit

OXAZOLIDINONES
(Linezolid, Tedizolid)

	LINEZOLID	TEDIZOLID
FDA Approval	2000	2014
timicrobial Spectrum of Activity	**Resistant Gram-positive bacteria** (MRSA, Vancomycin-resistant *Enterococci, CoNS,* Penicillin-resistant *Pneumococci)*	**Resistant Gra positive bacte** (esp. linezoli resistant strain *Staphylococc spp., Streptoco spp.*, *Enteroco spp.* and Penic resistant *Pneumococ*

	LINEZOLID	TEDIZOLID
Clinical Indications	Adults and **children** with complicated bacterial skin and skin structure infections **	Acute bacterial and skin struct infections in ad
Dose	Adults and adolescents ≥ 12 yrs: 600 mg bid Children (birth - 11 yrs): 10 mg/kg q 8 hrs	200 mg once da 6 days
Preparation	Infusion 2mg/ml 600 mg tab 100 mg/5 ml suspension	200 mg vial and mg tab
Cost	P4160.86/infusion bag P 3770/tab P 18,162.98/bottle	$1692 (IV) $2212(oral) ** for 6 day ther
ilability in the Philippines	Yes	No

Linezolid

Active against **resistant Gram-positive bacteria**

- MRSA, Vancomycin-resistant Enterococci, CONS and Penicillin-resistant Pneumococ

Bacteriostatic drug available in oral and IV form

Recommended for adults and **children** with Gram-positive SSTIs

Pediatric Data: Linezolid

Randomized studies have shown that Linezolid
ffective in curing complicated and uncomplicate
kin and soft tissue infections (SSTIs) in children

- Cure rate in **complicated** SSTIs (N=120, age <
  - Linezolid 85.7% vs Vancomycin 90.5%
    - Yogev R, et al. Pediatr Infect Dis J. 2003:22(9 suppl):
      S127
- Cure rate in **uncomplicated** SSTIs (N=455, age
  5-11)
  - Linezolid 88.7% vs Cefadroxil 86.2%
    - Wible K, et al. Pediatr Infect Dis J. 2003:22:315

Tedizolid

Oxazolidonine derivative approved by FDA in 014

Active against resistant Gram-positive acteria,esp. against linezolid-resistant strains *Staphylococcus spp., Streptococcus spp.*, *Enterococcus spp.* and Penicillin-resistant *Pneumococci*

Available in oral and IV forms

Not yet available in the Philippines

Tedizolid

Clinical studies in **adults** with acute bacterial skin and skin-structure infections

- A short 6-day course of tedizolid was **as effective** as a 10-day course of linezolid in terms of both early and sustained clinical responses

- Lowest effective dose: 200 mg OD
  - Prokocimer P, et al. JAMA 2013, 309:559

NO PEDIATRIC DATA

GLYCOPEPTIDES (Telavancin, Dalbavancin, Oritavancin)

	TELAVANCIN	DALBAVANCIN	ORITAVANCI
FDA Approval	2009	May 2014	August 2014
Antimicrobial Spectrum of Activity	**Gram-positive bacteria, incldg MRSA, CoNS, VSE and VRE**	**Gram-positive bacteria**, incldg MSSA, MRSA, MSSE, MRSE and enterococci; **poor activity v.s. VRSA**	**Gram-positiv bacteria**, inclc MRSA, VISA VRSA, daptomycin- nonsusceptibl S. aureus and VRE
	Penetrates epithelial lining fluid and alveolar macrophages		

	TELAVANCIN	DALBAVANCIN	ORITAVANCI
Clinical Indications	Nosocomial pneumonia, incldg VAP suspected or known to be caused by MRSA; cSSSIs	Acute bacterial skin and skin structure infections	Acute bacteria skin and skin structure infections
	Bactericidal concentration-dependent killing	Bactericidal concentration-dependent killing	Bactericidal concentration dependent killing
Dosing	Once daily administration	1000 mg on day 1 and 500 mg on day 8 (2 doses one week apart)	Single dose

Telavancin

Vancomycin-derived lipoglycopeptide

Potent bactericidal activity against Gram-posit
bacteria, including MRSA and CoNS

Penetrates pulmonary epithelial lining fluid and
alveolar macrophages

In vitro activity is unaffected by pulmonary
surfactant

Telavancin

linical studies in **adults**

- Similar efficacy and safety of Telavancin compared vancomycin in the treatment of **nosocomial pneumonia**
- Similar efficacy and tolerability of Telavancin compared to standard anti-staphylococcal beta-lactams and vancomycin for treating **complicated skin and skin-structure infections (cSSTIs)**
- Clinical response outcomes are non-inferior to vancomycin in the treatment of **HAP due to Gram-**

Pediatric Data: Telavanci

Pharmacokinetic study in paediatric patients
ged 1 to 17 years is currently on-going (as of
October 2015)

Dalbavancin

New lipoglycopeptide approved by FDA in May 2014

Demonstates in vitro activity against Gram-positive pathogens, incldg MSSA, MRSA, MSSE, MRSE and enterococci

Not active against vancomycin-resistant S. aureus

Dalbavancin

ong half-life and >90% protein binding allow a
osage regimen of 2 doses one week apart

linical studies in adults show non-inferiority to
ancomycin followed by oral linezolid in the
reatment of acute bacterial SSSTIs

- **Boucher HW, et al. N Engl J Med. 2014;370:2169-2179.**

uture studies on additional indications, i.e.
ospitalised community acquired pneumonia
CAP) and **paediatric osteomyelitis**

Oritavancin

ong half-life (about 250 hours) allows for sing
ose regimen to treat acute bacterial skin and
kin structure infections

linical studies in adults show non inferiority to
ancomycin in the treatment of ABSSSIs

- Corey GR, et al. Clin Infect Dis. 2015;60:2
  262

NO PEDIATRIC DATA

LIPOPEPTIDES

Daptomycin

Bactericidal, concentration-dependent
lipopeptide administered once daily

Indicated for adults with complicated SSTIs,
right-sided endocarditis due to S. aureus
(MRSA), and associated bacteremia

Drug is inactivated by surfactant, hence is not
recommended for pneumonia

Daptomycin

Currently not approved for use in children
but growing evidence supports its use in
children who have not responded to other
therapies for MRSA

Locally available as 500 mg/10 ml infusion (
400/infusion)

ediatric Data: Daptomyci

fficacy in children with **complicated SSTIs** EU-CORE Registry Data)

- Retrospective,post-marketing, non-interventional registry in 18 countries (2006-2012)
- 81 children (median 13 years, 24% with MRSA)
- Daptomycin has a **high clinical success rate whe given as both** first-line (93%) and second-line treatment (92%)
  - **Syriopoulou V, et al. ECCMID 2015. Abstract**

ediatric Data: Daptomyci

fficacy in children with **complicated SSSTIs**

- Randomized study of 396 children treated with Daptomycin vs standard of care (Clindamycin or Vancomycin)
- Age-adjusted dosing: 12-17 years = 5 mg/kg; 7-11 ye = 7 mg/kg; 2-6 years = 9 mg/kg; 1-<2 years = 10 mg/k
- Results: Daptomycin is **as effective** as standard of ca and requires fewer days of IV therapy (<3 days) before oral conversion
  - **Glasser C, et al. ESPID 2015. Abstract**

SA Guidelines

	• **Primary:** – Vancomycin 40 mg/kg/day – Clindamycin 40 mg/kg/day • **Alternative:** – Linezolid 10 mg/kg/dose < age 12; 600 mg/dose > ag
remia and ve arditis	• **Primary:** Vancomycin 15 mg/kg/dose • **Alternative:** Daptomycin 6-10 mg/kg/dose
myelitis and arthritis	• **Primary:** – Vancomycin 40 mg/kg/day – Clindamycin 40 mg/kg/day • **Alternative:** – Daptomycin 6 mg/kd/day – Linezolid 10 mg/kg/dose < age 12; 600 mg/dose > ag

...ernative Therapy to Vancomycin for ...RSA

...aptomycin

- Concentration-dependent killing
- Bactericidal
- Once-daily administration

...eftaroline/Ceftobiprole

- Bactericidal
- 2-3-daily administrations

...nezolid

- Bacteriostatic
- Twice-daily administration

...elavancin

- Concentration-dependent killing
- Bactericidal
- Once-daily administration

- **Teicoplanin**
  - Bactericidal
  - Once-daily administration
- **Dalbavancin**
  - Concentration-dependent killin
  - Bactericidal
  - 1st and 8th day (ABSSSI)
- **Tedizolid**
  - Bacteriostatic
  - Once-daily (ABSSSI)
- **Oritavancin**
  - Concentration-dependent killin
  - Bactericidal
  - Single-dose (ABSSSI)

CEPHALOSPORINS (Cefaroline, Ceftobiprole,Ceftolozane-Tazobactam, Ceftazidime-Avibactam)

	FOSAMIL	CEFTOBIPRO
FDA Approval	2010	2014
timicrobial Spectrum of Activity	**"Fifth-generation cephalosporin"** (expanded **Gram-positive activity),** incldg **MRSA, VRSA**, S. pneumoniae, Strep. pyogenes, as well as **Gram-negative spp.**(Haemophilus influenzae and Moraxella catarrhalis, incldg resistant strains) **The only FDA approved cephalosporin with activity against VISA**	**"Fifth-generat cephalospori** (expanded **Gra positive activi incldg MRSA** well as non-Be lactamase produ Gram-negativ organisms The most pote cephalosporin te against S. pneumoniae

Ceftaroline fosamil

Bactericidal, parenteral cephalosporin with expanded **Gram-positive activity**, incldg VRSA and MRSA

"fifth-generation" cephalosporin

Active against **Gram-positive organisms** (S. pneumoniae, S. aureus, incldg MRSA and S. pyogenes) and **Gram-negative species** (H. influenzae and Moraxella catarrhalis, incldg. resistant strains)

Ceftaroline fosamil

Clinical trials demonstrate non-inferiority to the standard of care for the treatment of communi acquired pneumonia (CAP) and skin and skin tructure infections (SSSIs)

- Corey GR, et al. Clin Infect Dis. 2010;51:64 650
- File TM Jr, et al. Clin Infect Dis. 2010;51:13 1405.

ow potential for resistance development

Ceftaroline fosamil

Favorable safety and tolerability profile

Currently NOT RECOMMENDED for children
8 years

Safety and efficacy study of Ceftaroline vs
omparator in paediatric patients with CAP ha
een completed (unpublished)

Ceftobiprole

Clinical trials showed non-inferiority to comparator drugs in the treatment of cSSSIs and hospitalised CAP patients

- Nicholson SC, et al. Int J Antimicro Agents 2012, 39(3): 246.

	CEFTOLOZANE TAZOBACTAM	CEFTAZIDIM AVIBACTA
FDA Approval	December 2014	February 201
timicrobial Spectrum of Activity	Excellent in vitro activity against ***Pseudomonas aeruginosa*** strains, incldg **cephalosporin- and carbapenem-resistant isolates** Good to excellent activity against other **Gram-negative** organisms, incldg ESBL-producing enterobacteriaceae such as ***E. coli and K. pneumoniae***	• **Avibactam** - new Beta-lactamase inhibitor that extends activ to ESBL and AmpC produ **Gram-negati strains**, as w as to some carbapenema

	CEFTOLOZANE-TAZOBACTAM	CEFTAZIDIM AVIBACTAM
Clinical Indications	Complicated intra-abdominal infections (cIAIs) in combination with metronidazole Complicated urinary tract infections in adults	Complicated intr abdominal infecti (cIAIs) in combina with metronidaz Complicated urir tract infections adults
Pediatric Data	**None**	None

GLYCYLCYCLINE
(Tigecycline)

Tigecycline

Broad-spectrum glycylcycline antibiotic used fo
treating serious bacterial infections in adults

Available as 50 mg/5 ml infusion (3529)

ediatric Data: Tigecyclin

hase II, multicenter, open-label clinical trial on
harmacokinetics and safety profile of tigecycline

3 children (8-11 years) with **community-acquired**
neumonia, complicated intra-abdominal infections
cIAI), or complicated skin and skin structure infecti
cSSSI)

onclusion: A dosage of 1.2 mg/kg q 12h may represent
e most appropriate dosage for subsequent evaluation
hase III clinical trials in children with selected serious
acterial infections

- **Purdy J, et al. Clin Ther. 2012 Feb;34(2):49**

CARBAPENEMS

Imipenem, Meropenem, **Ertapenem**

Provide the BROADEST spectrum of activity c
currently approved antibiotics

Active against gram-positive bacteria,
naerobes, gram-negative bacteria (including
most ESBL producers), anti-Pseudomonas
overage

NOT ACTIVE against *Stenotrophomonas*
naltophilia, MRSA, Enterococcus faecium

Classification of Carbapenems

	GROUP 1	GROUP 2	GROUP
Carbapenems	**Ertapenem** Panipenem Tebipenem	**Imipenem** **Meropenem** **Doripenem** Biapenem	Tomopen Razupen
vity against non-fermentants ***udomonas aeruginosa and*** ***Acinetobacter baumanii)***	No	Yes	Yes
Activity against **MRSA**	No	No	Yes

	ERTAPENEM	DORIPENE
FDA Approval	2001	2007
timicrobial Spectrum of Activity	Less action on *Pseudomonas aeruginosa and Acinetobacter*	Similar to imipe and meropene
ntimicrobial resistance potential	High	Low

	ERTAPENEM	DORIPENE
Pediatric Dosing	**3 mos-12 yrs**: 15 mg/kg q 12 hrs **≥ 12 yrs**: 1 gm q day IV or IM	**3 mos - < 2 yrs** mg/kg q 8 hrs **≥ 2 yrs**: 15 mg/ 8 hrs* (max 5 mg/dose
Preparation	1 gm powder for injection	500 mg infusi
Cost	3016.02/vial	2500/vial

*Further studies on dosing intervals of Doripenem are

Ertapenem

linically indicated for the following moderate to evere infections in adults

- Acute pelvic infections, community-acquired pneumonia, complicated intra-abdominal infections, complicated skin and skin structure infections, complicated urinary tract infections

ff-label Indications

- Treatment of IV catheter-related bloodstream

Pediatric Data: Ertapener

wice daily dosing regimens for children ≤ 12 years

Comparable efficacy to Ceftriaxone in the treatment
rinary tract infections, skin and soft-tissue
nfections and community-acquired pneumonia

- **Arguedas A, et al. ICAAC 2005.Abstract G-**
- **Arguedas A, et al. Int J Antimicrob Agents.**
  2009

Comparable efficacy to ticarcillin-clavulanate in the
eatment of **paediatric intra-abdominal and pelvi**
nfections

- **Johnson J, et al. ICAAC 2005.Abstract G-9**

Doripenem

Main clinical indications in adults

- Complicated UTIs, complicated intra-abdominal infections, hospital-acquired pneumonia, ventilator-associated pneumo

Currently recommended only for those > 18 years of age

Pediatric Data: Doripener

Efficacy and safety multicenter study conducted in Japan

100 pediatric patients (2 mos - 13 yrs) with pneumonia, UTI, otitis media, septicaemia, and other severe paediatric infections

Conclusion: Doripenem 20 mg/kg 2x or 3x a day was **clinically effective and well-tolerated** in treating paediatric infections

- **Sunakawa K, et al. ICAAC 2011. Abstract G3-**

ew Antibiotics approved and/o in development

Cephalosporins **eftaroline fosamil, Ceftobiprole, Ceftolozane/Tazobactam**)	**Oxazolidinones** (**Tedizolid**, Radezolid)
Carbapenems (Panipenem, Biapenem, Razupenem, Tomopenem, Tebipenem/pivoxil)	**Glycopeptides** (**Oritavancin, Telavancin, Dalbavancin**)
Monobactams (BAL30072)	**Polymixin** (CB-182,804)
Aminoglycosides (Plazomicin)	**Tetracycline** (Eravacycline, Omadacycline)
Quinolones	**Pleuromutilin compound**

SUMMARY

Resistance is the driver for new antibiotics

New antibiotics will greatly contribute to effecti
management of infections caused by the usua
but increasingly multidrug-resistant bacteria

Clinical studies in adults demonstrate safety a
efficacy

Few or no paediatric data are available

Thank You