The AIDA Project

Prof. dr. Johan W. Mouton

ARTE
Antimicrobial Resistance Therapeutics and molecular Epidemiology

Erasmus MC

Grant Health-F3-2011-278348

AIDA – Antimicrobial Resistance in Gram-Negatives

- General Europe-wide increase of resistance in gram-negative pathogens (e.g. *E. coli, K. pneumoniae* and *P. aeruginosa).*
- Significant increase in MDR in K. pneum. and E. coli in more than one-third of the EU/EEA countries.
- In several Member States, 25 % - >60% of K. pneum. are MDR.

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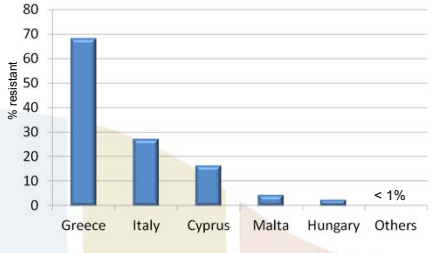
AIDA – Antimicrobial Resistance in Gram-Negatives

- *K. pneumoniae:* Carbapenem resistance (=extensively resistant)



EARS-net report 2011

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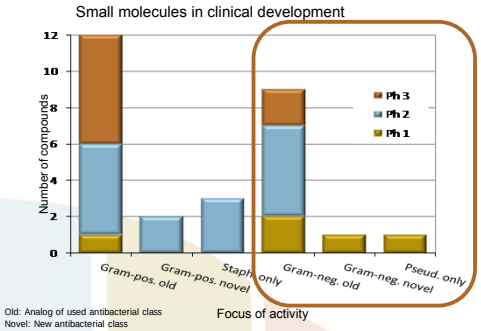
AIDA – Dry R&D Pipelines



U. Theuretzbacher: IJAA, 2012, 39:295– 299 (updated)

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AIDA – Other potential solutions?

- Redeveloping old antibiotics as if they were new:
  - what is their true value?
  - Are some drugs better than others?
- Combinations of antibiotics useful?

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The meeting so far

- Presentations focussing on development of new antibiotics
- Several lead candidates shown
- Activity of some of these may be promising

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Efficacy of an Antimicrobial

Potency of a drug
(MIC)

Exposure to the bug
In vivo
(PK)

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ACTIVITY
in vitro

CONCENTRATIONS
***in vivo* (PK)**

DOSING REGIMEN

ANTMICROBIAL EFFECTIVENESS
(*Microbiological Cure*)

Other factors

CLINICAL EFFICACY
(*Clinical Cure*)

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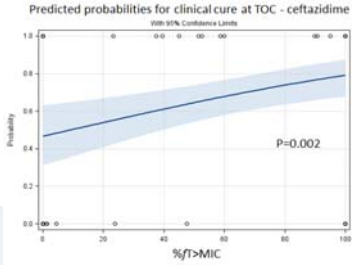
EFFICACY IS DEPENDENT ON BOTH POTENCY AND PK (AND many other factors)



Probability plot of the logistic regression analysis for ceftazidime showing the relationship between %fT>MIC (Gram-negatives at baseline/EOT) and probability of cure at TOC

Muller et al, JAC 2013 68:900-906

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Clinical development of new drug essentials

Potency

↓

PK profiling

↓

Dose

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Clinical Development of old drug essentials

Potency

↓

PK profiling

↓

Dose

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7 major steps For Dosefinding

STEP	ACTION
1	Establish PK/PD index that is correlated with effect of DRUG
2	Establish the pharmacodynamic target of DRUG in animals (mice)
3	Determine is protein binding in mice and in humans of DRUG
4	Determine the wild type (WT) distribution of micro-organisms to be covered
5	Set the highest MIC that proposed dosing regimens are required to cover (usually the highest ECOFF of target micro-organisms)
6	Establish the dose – exposure relationship of the drug
7	Determine dosing regimens that cover target micro-organisms

Mouton handbook pkpd 2014

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Studies for 7 major steps For Dosefinding

STEP	ACTION	METHODS
1	Establish PK/PD index that is correlated with effect of DRUG	Time-kill studies; Preclinical studies in animals and IVPM; PD modeling
2	Establish the pharmacodynamic target of DRUG	Interpretation of models in step 1 (neutropenic vs non-neutropenic animals; static effects; 1 or 2 log kill effects)
3	Determine is protein binding in mice and in humans of DRUG	Protein binding in mice and men over full concentration range expected
4	Determine the wild type (WT) distribution of micro-organisms to be covered	Epidemiological studies of target-micro-organisms (surveys)
5	Set the highest MIC that proposed dosing regimens are required to cover (usually the highest ECOFF of target micro-organisms)	Review and interpret survey results
6	Establish the dose – exposure relationship of the drug	Phase 1 studies – single and multiple dose; dose escalation
7	Determine dosing regimens that cover target micro-organisms	Population pharmacokinetic analysis; Monte Carlo simulations

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Pharmacodynamics

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

5. Pharmacodynamics				
fAUC/MIC for bacteriostasis				
fAUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comments	• Pharmacodynamic parameters for nitrofurantoin have not been determined. • Cells are left empty when data are not readily available.			
References				

Nitrofurantoin: Rationale for the EUCAST clinical breakpoints, version 1.0,2010

AIDA – Other potential solutions?

- Redeveloping old antibiotics as if they were new:
  - what is their true value?
  - Are some drugs better than others?
- Combinations of antibiotics useful?
  - Systematic reviews
  - Clinical trials

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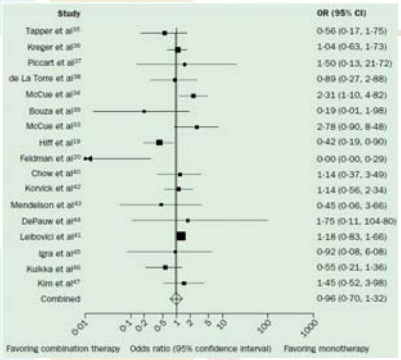
Antibiotics

"If one is good two must be better"

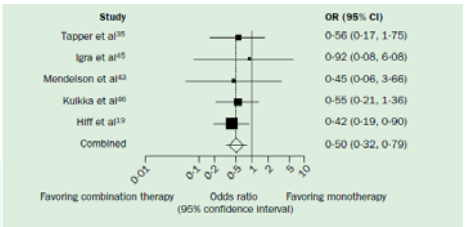
Why combination therapy?

- Increased spectrum of coverage –independent
- Increased spectrum of coverage –fixed
  - Amoxicillin/ clavulanic acid
- Penetration at different sites of infection
- Synergism: increased activity of the antimicrobials



Safdar et al., Lancet Infect Dis 2004

Pseudomonas only – reduction in mortality



Safdar et al., Lancet Infect Dis 2004

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Paul et al, BMJ 2004 : 64 trials — no difference in outcome
increase in toxicity (aminoglycosides)

Safdar et al, LID 2004 : 17 trials — no difference in outcome
except pseudomonas

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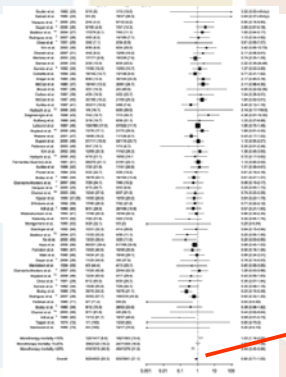

Survival for serious infections associated with sepsis and septic shock

0.86 (0.71-1.03)

Kumar et al CCM 2010

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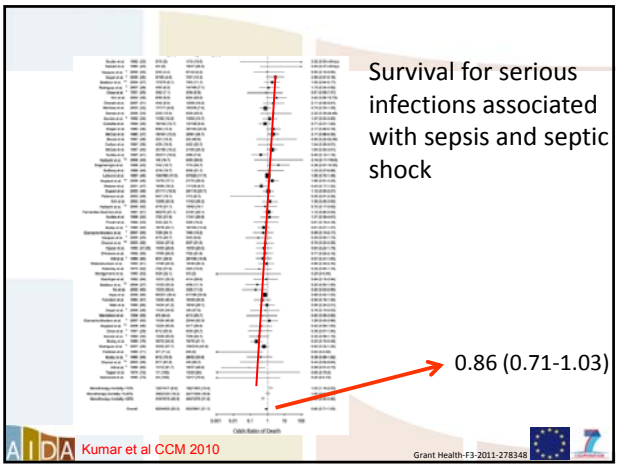
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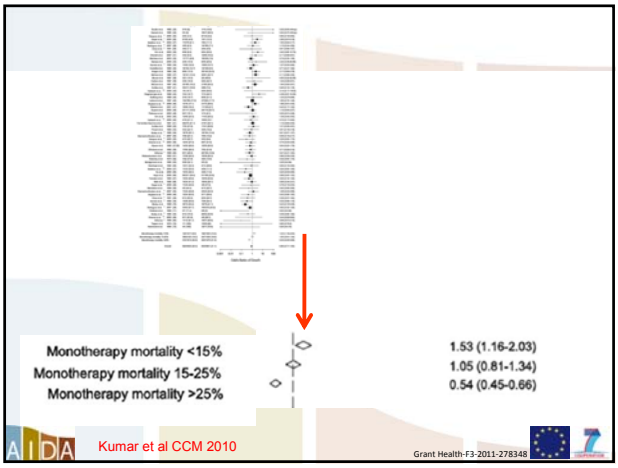
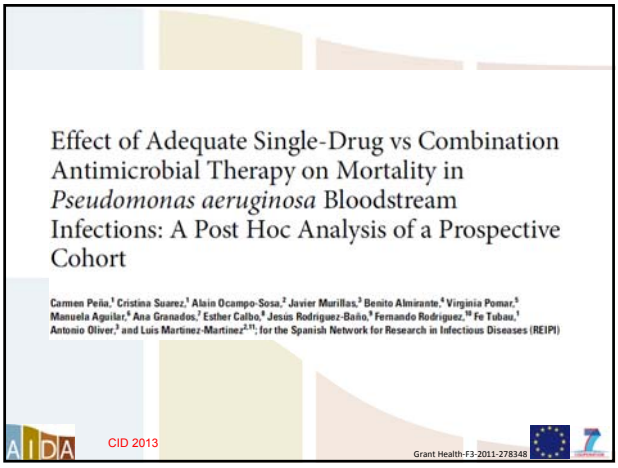

Monotherapy mortality <15%
Monotherapy mortality 15-25%
Monotherapy mortality >25%
1.53 (1.16-2.03)
1.05 (0.81-1.34)
0.54 (0.45-0.66)
Kumar et al CCM 2010
Grant Health-F3-2011-278348


Effect of Adequate Single-Drug vs Combination Antimicrobial Therapy on Mortality in *Pseudomonas aeruginosa* Bloodstream Infections: A Post Hoc Analysis of a Prospective Cohort
Carmen Peña,[1] Cristina Suarez,[1] Alain Ocampo-Sosa,[2] Javier Murillas,[3] Benito Almirante,[4] Virginia Pomar,[5] Manuela Aguilar,[6] Ana Granados,[7] Esther Calbo,[8] Jesús Rodriguez-Baño,[9] Fernando Rodriguez,[10] Fe Tubau,[1] Antonio Oliver,[3] and Luis Martinez-Martinez[2,11], for the Spanish Network for Research in Infectious Diseases (REIPI)
CID 2013
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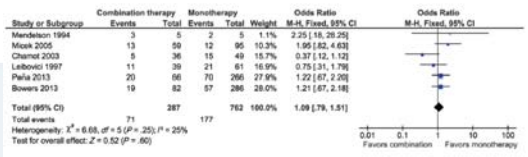
Clinical evidence – Gram-negatives

> 6 meta analyses of clinical trials
show no superiority of beta-lactam + aminoglycoside to beta-lactam alone for the treatment of sepsis, fever eci etc.

Combination Therapy for *Pseudomonas aeruginosa* Bacteremia: Where Do We Stand?

Mical Paul[1,2] and Leonard Leibovici[2,3]

[1]Unit of Infectious Diseases, Rambam Health Care Campus, Haifa; [2]Sackler Faculty of Medicine, Tel-Aviv University, Ramat Aviv, and [3]Department of Medicine E, Rabin Medical Center, Petah-Tikva, Israel



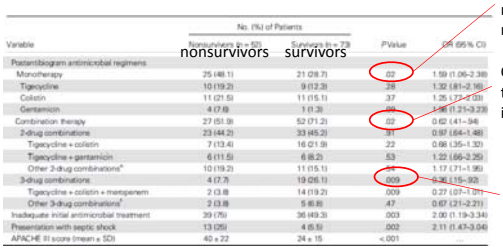
CID 2013

Treatment of KPC-producing K. pneumoniae strains

- multicenter retrospective cohort study, (3 large Italian teaching hospitals)
- 125 patients with bloodstream infections caused by KPC-producing Kp
- Outcome: death within 30 days of the first positive blood culture
- Analysis:
  - Monotherapy vs combination therapy?
  - Other factors influencing outcome?

Tumbarello, CID,2012;55(7):943–50

Univariate analysis antibiotic regimen



Variable	No. (%) of Patients: nonsurvivors (n = 52)	No. (%) of Patients: survivors (n = 79)	P Value	OR (95% CI)
Postantibiogram antimicrobial regimens				
Monotherapy	25 (48.1)	21 (26.7)	.02	1.59 (1.06–2.38)
Tigecycline	10 (19.2)	9 (12.3)	.28	1.32 (.81–2.16)
Colistin	11 (21.5)	11 (15.1)	.37	1.25 (.77–2.03)
Gentamicin	4 (7.6)	1 (1.3)	.03	2.92 (1.21–3.23)
Combination therapy	27 (51.9)	52 (71.2)	.02	0.62 (.41–.94)
2-drug combinations	23 (44.2)	33 (45.2)	.91	0.97 (.64–1.48)
Tigecycline + colistin	7 (13.4)	16 (21.9)	.22	0.68 (.35–1.32)
Tigecycline + gentamicin	6 (11.5)	6 (8.2)	.53	1.22 (.66–2.25)
Other 2-drug combinations[a]	10 (19.2)	11 (15.1)	.52	1.17 (.71–1.95)
3-drug combinations	4 (7.7)	19 (26.1)	.009	0.24 (.15–.90)
Tigecycline + colistin + meropenem	2 (3.8)	14 (19.2)	.009	0.27 (.07–1.01)
Other 3-drug combinations[a]	2 (3.8)	5 (6.8)	.47	0.67 (.21–2.21)
Inadequate initial antimicrobial treatment	39 (75)	36 (49.3)	.003	2.00 (1.19–3.34)
Presentation with septic shock	13 (25)	4 (5.5)	.002	2.11 (1.47–3.04)
APACHE III score (mean ± SD)	40 ± 22	24 ± 15	< .001	…

nonsurvivors

survivors

Monotherapy more in nonsurvivors

Combination-therapy more in survivors

3-drug Combination-therapy even more significant

Tumbarello, CID,2012;55(7):943–50

Multivariate analysis

- outcome independently predicted by 3 factors:
  - presence of septic shock
  - high APACHE III score
  - **inadequate empirical therapy**
- **Supports combination therapy mainly to an increase antimicrobial spectrum**

AIDA Tumbarello, CID,2012;55(7):943–50

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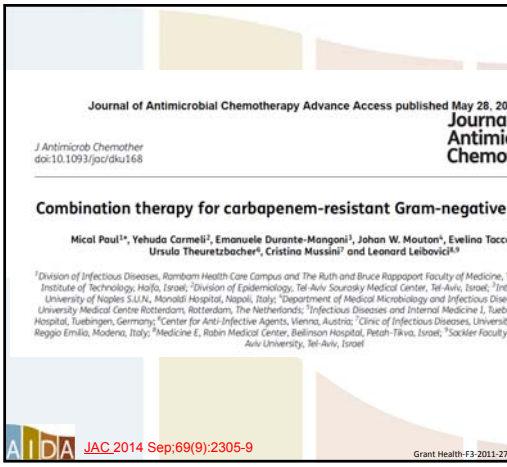

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J Antimicrob Chemother
doi:10.1093/jac/dku168

Journal of Antimicrobial Chemotherapy

Combination therapy for carbapenem-resistant Gram-negative bacteria

Micol Paul[1]*, Yehuda Carmeli[2], Emanuele Durante-Mangoni[3], Johan W. Mouton[4], Evelina Tacconelli[5], Ursula Theuretzbacher[6], Cristina Mussini[7] and Leonard Leibovici[8,9]

[1]Division of Infectious Diseases, Rambam Health Care Campus and The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel; [2]Division of Epidemiology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; [3]Internal Medicine, University of Naples S.U.N., Monaldi Hospital, Napoli, Italy; [4]Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands; [5]Infectious Diseases and Internal Medicine I, Tuebingen University Hospital, Tuebingen, Germany; [6]Center for Anti-Infective Agents, Vienna, Austria; [7]Clinic of Infectious Diseases, University of Modena and Reggio Emilia, Modena, Italy; [8]Medicine E, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel; [9]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

AIDA JAC 2014 Sep;69(9):2305-9

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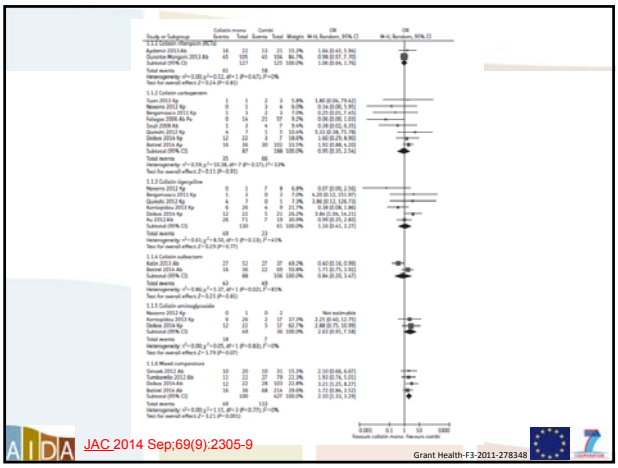

JAC 2014 Sep;69(9):2305-9

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P vs. PC: all-cause mortality

- A single retrospective study in Brasil presented an adjusted analysis
- 83% *A. baumannii*, all CR.
- Polymyxin B (~ 152mg/d no loading dose) vs. P + meropenem (3 gr/d)
- HR for mortality with combination therapy 0.4 (95% CI 0.2-0.81), adjusted for APACHE II at polymyxin B onset, creatinine clearance ≥60ml/min and polymicrobial infection.

Rigatto et al. AAC 2015

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AIDA – Preserving Antibiotics for the Future

- Assessment of clinical efficacy by a pharmacokinetic/ pharmacodynamic approach to optimize effectiveness and reduce resistance for off-patent antibiotics
- 16 partners from 11 different countries

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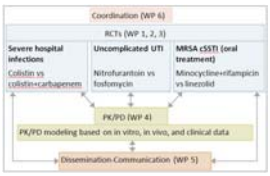
AIDA – From Bench to Bedside and Back

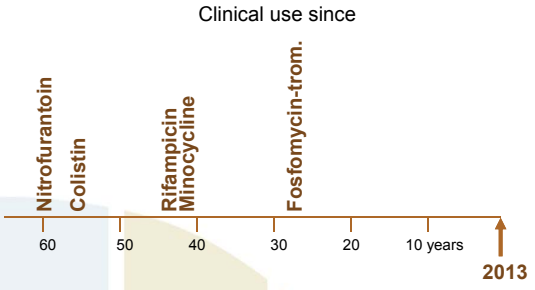
- 3 areas of bacterial diseases
  - Severe hospital infections
  - Uncomplicated UTI
  - MRSA cSSTI
- 5 antibacterial drugs
  - Colistin
  - Nitrofurantoin, fosfomycin
  - Minocycline, rifampicin



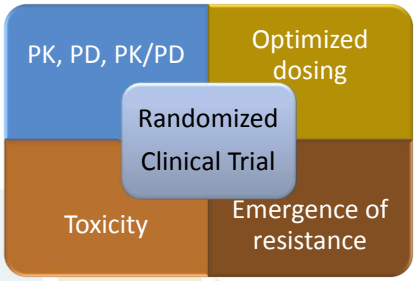
AIDA – Antimicrobial Resistance in Gram-Negatives

- General Europe-wide increase of resistance in gram-negative pathogens (e.g. *E. coli, K. pneumoniae* and *P. aeruginosa).*
- Significant increase in MDR in K. pneum. and E. coli in more than one-third of the EU/EEA countries.
- In several Member States, 25 % - >60% of K. pneum. are MDR.

AIDA – Use of Old Antibiotics



AIDA – "Re-Development" of Old Antibiotics



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AIDA – Colistin trial

- **WP 1 - Colistin vs Colistin + Meropenem**
- Multicenter, open-label, randomised clinical trial to compare colistin alone vs. colistin plus meropenem for severe infections caused by carbapenem-non-susceptible bacteria.
- This randomised clinical study will show whether the addition of a carbapenem improves the clinical outcome in severe infections caused by carbapenem non-susceptible bacteria. So far, only limited observational data are available. PK/PD models de-veloped in WP4 analyse individual patient's serum concentrations, link them to microbiological results and refine data and guidance for dosing decisions. The microbiological package will monitor and analyse information about potential emergence of resistance.
- Progress of WP1:
  - Three centers in Israel, two in Greece and one in Italy are recruiting critically ill patients with microbiologically documented carbapenem-non-susceptible and colistin-susceptible Gram-negative bacteria.
  - Serum samples are collected and processed for PK analysis (WP4). Physiologically-Based PK modeling will be used to characterise colistin tissue distribution.

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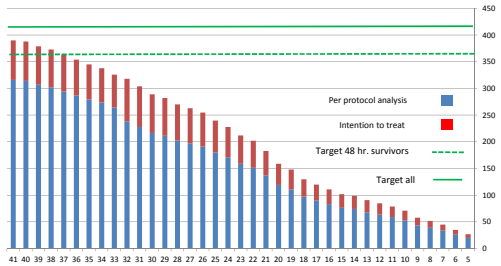
Recruitment Status - 31 October 2016

- Original sample size calculation: 360 patients
- Revised sample size: 360 48-hour survivors (total 414 patients)



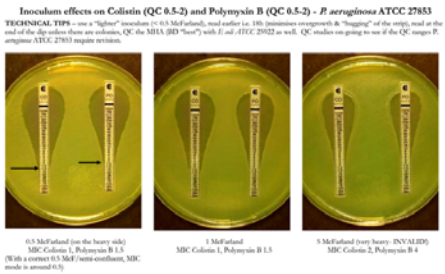
AIDA – Colistin trial

- Inclusion nearly finished
- 1st analysis of colistin and meropenem PK done
- Very high mortality in both groups
- NIH trial collaborations
- In vitro combination tests predictive?

AIDA

Colistin susceptibility testing – some issues (but not all)

An MIC is an MIC is an MIC.....is not it?



In vitro testing

Microbroth dilution, E-test, disc dilution used to test Polymyxin B.

10 strains *A.baumannii* (MIC 0.25-4mg/L)

10 strains *P.aeruginosa* (MIC ≤0.25 – 1mg/L)

4 Muller-Hinton Broth/Agars Oxoid, Difco, Merck, Himedia

	Broth micro dilution	MIC (mg/L) range E-Test			
		Oxoid	Difco	Merck	Himedia
Acinetobacter	0.25-4	0.5-16	0.3-6	0.12-1.5	0.38-4
% ± 1 log_2		80	100	80	90
P.aeruginosa	≤0.25-1	0.5-4	1.5-2	0.06-0.5	0.75-3
% + 1 log_2		20	40	70	10

Giardello et al, 2012

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In vitro testing - Ion concentration is MH broth and agar

		Ion concentration (Mg/L)	
		Ca	Mg
CLSI parameters		20-25	10-12.5
Muller Hinton Agar	Oxoid	20.9	13.3
	Difco	16.1	4.9
	Merk	7.5	6.2
	Hinedra	25.3	31.2

Significant variation in MICs on MHA and Ca or Mg concentrations across different agars

Giardello et al, 2012

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Colistin binding – impact of microtitre tray on MIC

Species	Microtitre plate	MIC distribution 0.015	0.03	0.06	0.12	0.25	0.5	1.0	2.0	4.0	8.0
P.aeruginosa (n=56)	V bottom	0	0	0	0	8	31	14	3	0	0
	tissue culture	0	0	0	0	0	1	4	44	6	1
Acinetobacter sp (n=29	V bottom	0	0	1	3	13	8	2	0	2	0
	tissue culture	0	0	0	0	0	2	3	15	5	6
Enterobacteriaceae (n=61)	V bottom	0	0	1	2	38	20	0	0	0	0
	tissue culture	0	0	0	0	0	10	28	17	6	0

Albur et al, 2012

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Colistin – testing issues

- . Susceptibility dependent on medium, plastic
- Several studies
- . Standard testing protocol published last year as a collaboration between CLSI, EUCAST
- All strains in AIDA are stored for retesting…

AIDA – WP3 Minocycline + Rifampicin vs. Linezolid

- Multicenter randomised controlled clinical trial to compare oral treatment with minocycline plus rifampicin to oral treatment with linezolid for acute bacterial skin and soft tissue infections due to MRSA.
- This clinical study aims at demonstrating non-inferiority between the two treatment regimens in terms of efficacy and safety. The results will allow correlating non-clinical PK/PD information with clinical outcome and validate the doses and combination used.

AIDA –WP3 Minocycline + Rifampicin vs. Linezolid

- . Study had to be redesigned twice because of inclusion problems.
- . Now finalizing inclusion
- PKPD package done

AIDA –WP2 Fosfomycin-Trometamol vs. Nitrofurantoin

- . Multicenter, randomised clinical trial to compare fosfomycin trometamol vs. nitrofurantoin for the treatment of uncomplicated lower urinary tract infection in women at high risk of multidrug-resistant pathogens. The increasing prevalence of ESBL-producing enterobacteriaceae with co-resistance to most commonly used antibiotics require well characterised alternative drugs to preserve their usefulness.
- This clinical study will assess the potential superiority of one of the two study drugs in a common condition aggravated by increasing multidrug-resistance. The risk of adverse events will be an important outcome measure.

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AIDA –WP2 Fosfomycin-Trometamol vs. Nitrofurantoin

- Study finalizing inclusion
- PK of nitrofurantoin and fosfomycin
- PD of nitrofurantoin and fosfomycin

- Susceptibility testing of fosfomycin in the routine lab – major problem, not yet solved. EUCAST method is almost there

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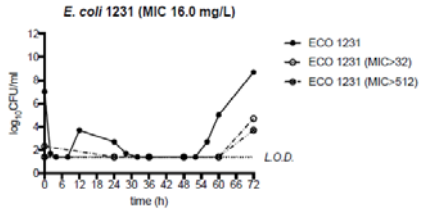
Fosfomycin – resistance development in a bladder model



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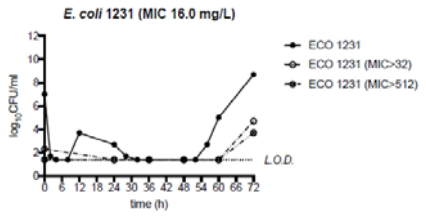
Fosfomycin – resistance development in a bladder model and hollow fiber models



Combinations may be required in near future…..

Unpubl.

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Conclusions

- After finding in vitro potency, there are many hurdles to take
- Combinations will be required – but the reasons are multiple
- Rational dosing of single drugs and combinations require team efforts

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