Reviving old antibiotics: the AIDA experience

Preserving old antibiotics for the future

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Re-developing process

- Identify the knowledge gaps, assess quality of information
- Use cutting-edge methods to close the knowledge gaps
- Share knowledge with regulatory agencies and policy makers
- Disseminate and communicate to the medical community and all stakeholders

AIDA: “Re-developing” of old antibiotics

14 partners from 11 different countries, complimentary expertise

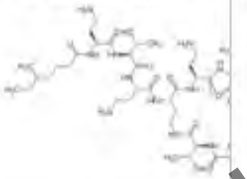
1912 - Paul Ehrlich

Paul Ehrlich discovers the first specific chemotherapeutic agent for a bacterial dise

Salvarsan for syphilis

1950 - Colistin

First usage of colistin

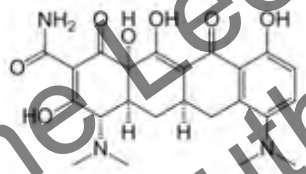


1967 - Rifampicin

Rifan

1972 - Minocycline

Minocycline approved



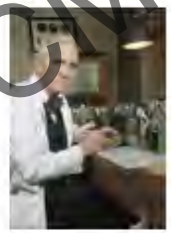
2012 - AIDA

AIDA starts the project to revive old but still effective antibiotics

1929 - Alexander

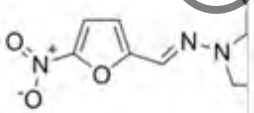
Alexander Fleming

penicillin



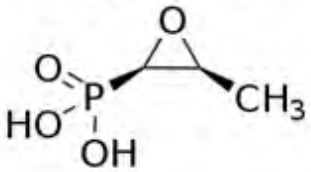
1953 - Nitrofurantoin

Nitrofurantoin became ava



1971 - Fosfomycin

Clinical usage of fosfomycin



1996 - KPC Carbapenemase described

First KPC-carbapenemase described. The beginning of the worldwide resistance threat in Gram-negative bacteria

“Re-developing” of old antibiotics: Principles

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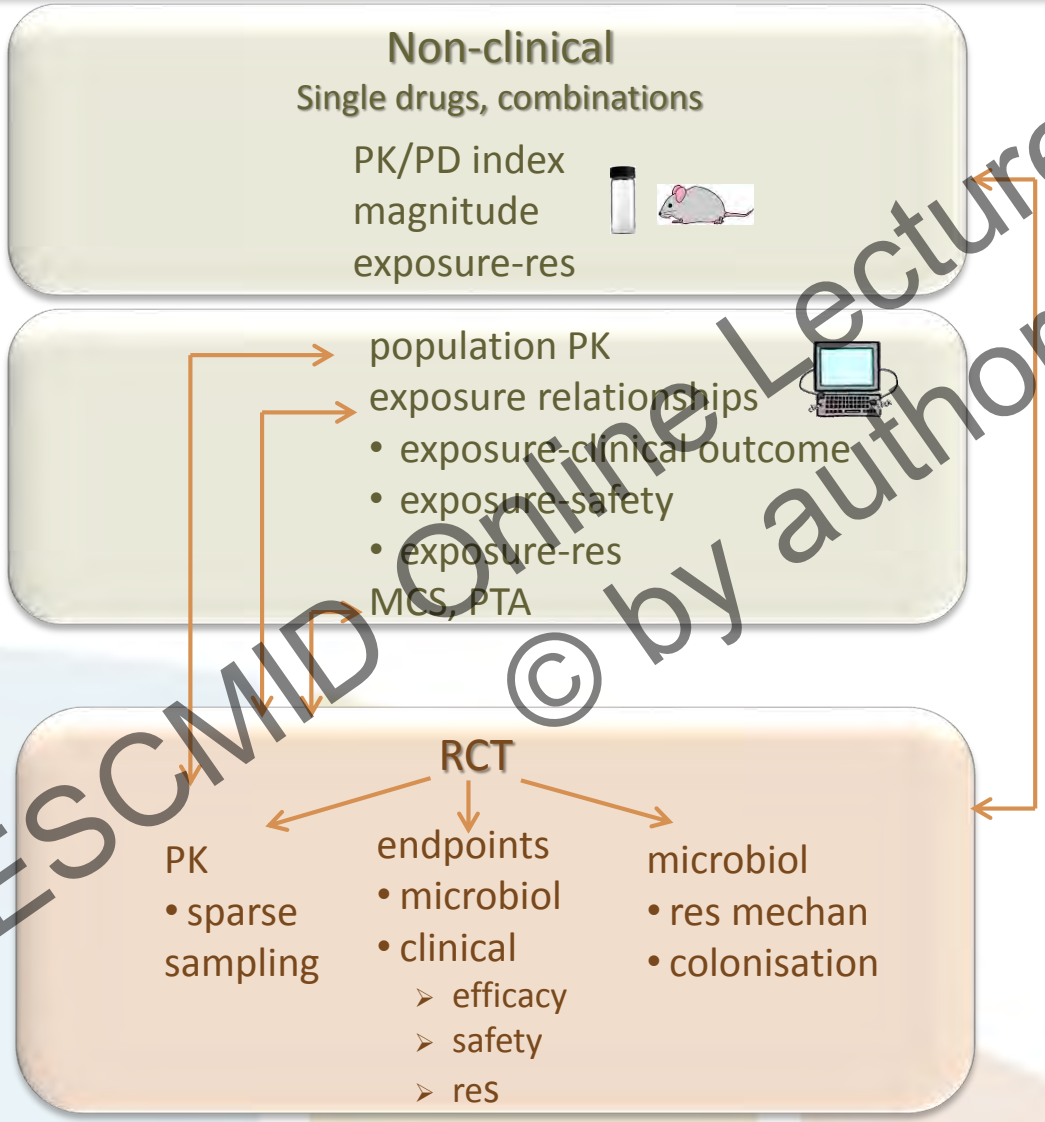

Aims:

- Dosing recommendations
- Efficacy (superiority, non-inferiority
- PK
- Safety
- Combination therapy
- Emergence of resistance
- Breakpoints
- Valid comparators for new antibiotics

“Re-developing” of old antibiotics: Colistin

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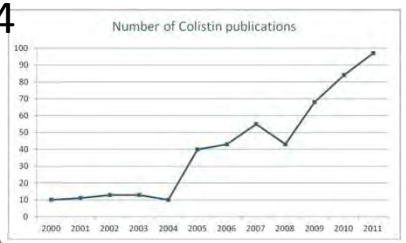
2010

Prior knowledge
<2004

Prior knowledge
>2004



Non-clinical studies

Optimised usage

Randomised controlled clinical trial in critically ill patients

PK

microbiology

outcome

Production
Regulation
Nomenclature

Current evolving knowledge

“Re-developing” of old antibiotics: Colistin

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Non-clinical studies

kill dynamics
single drug,
combination, synergy,
res. analysis
protein binding

PK/PD

population PK
PK/PD modeling+simulation

RCT

carbapenem resistant Gram-negative inf.
colistin alone vs. colistin + carbapenem

superiority | safety | emergence of resistance

Microbiology:
- MIC, synergy,
- colonisation;
- res. mechan.

PK
Sparse sampling

Exposure-
- efficacy-
- toxicity-
- resistance-
relationship

“Re-developing” of colistin: Challenges

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- Analytical issues
  - Measurement of concentrations
- Clinical trial in severely sick patients, superiority RCT
  - Informed consent
  - Diagnostics, pre-treatment
  - Lack of evidence and preconceptions
- Translating results to clinical practice
  - Regulatory, guidelines, training

“Re-developing” of colistin: Policy actions in Europe

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- SPC updated and harmonised
- Quality and production standards updated
- Animal farming/veterinary

“Re-developing” of colistin: Policy actions in Europe

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- Introduced dose content conversion table between CMS expressed in IU, CMS expressed in mg and CBA expressed in mg

Colistimethate sodium (IU)	Colistimethate sodium (mg)	Colistin-base activity (CBA) (mg)[1]
12 500	1	0.4
150 000	12	5
1 000 000	80	34
4 500 000	360	150
9 000 000	720	300

“Re-developing” of colistin: Policy actions in Europe

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- Adults: **9 M IU daily in 2 or 3 divided doses** as a slow iv infusion; in critically ill patients a **loading dose of 9 M IU** should be given. The most appropriate time interval to the first maintenance dose has not been established.
- Doses should be reduced according to creatinine clearance in patients with renal impairment.
- Modelling suggests that loading and maintenance doses of **up to 12 M IU** may be required in patients with good renal function in some cases. Clinical experience with such doses is however extremely limited, and safety has not been established.
- The loading dose applies to patients with normal and impaired renal functions including those on renal replacement therapy
- Children <40kg: 75,000 to 150,000 IU/kg daily, in 3 divided doses. The use of doses >150.000 IU/kg/day has been reported in children with cystic fibrosis. There are **no data** regarding the use or magnitude of a loading dose in critically ill children. No dose recommendations have been established in children with impaired renal function.
- Consideration should be given to **co-administration** with another antibacterial agent whenever this is possible.

“Re-developing” of colistin: Policy actions in Europe

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- Indicated for the treatment of serious infections due to selected aerobic Gram-negative pathogens in patients with limited treatment options

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EUCAST Breakpoints

	Susceptible (S)	Resistant (R) [a]
Acinetobacter	S≤2	R>2 mg/L
Enterobacteriaceae	S≤2	R>2 mg/L
Pseudomonas spp	S≤4	R>4 mg/L

[a] *Breakpoints apply to dosage of 2-3 MIU x 3. A loading dose (9 MIU) may be needed.*

“Re-developing” of old antibiotics: AIDA

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- Filling knowledge gaps
  - Critically sick patients with infections caused by extensively drug-resistant Gram-negative bacteria
  - Outpatient treatment of patients with acute lUTI and high risk of multi drug-resistant Gram-negative bacteria
  - Outpatient treatment of patients with acute skin- and soft tissue infections caused by MRSA
- Policy, regulatory, funding issues
- Communication, education