Real-time antimicrobial sensing – closing the loop on precision antimicrobial therapy

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Real time monitoring and closed-loop control

Declaration

• No conflicts to declare
Individualized antimicrobial therapy

- Challenges
- Antimicrobial biosensors
- Closed loop control
- New PK-PD targets
- Integrated systems
Dosing is a dynamic process

Inter-individual variability
- Race
- Weight
- Age
- Gender
- Medications
- Comorbidities

Intra-individual variability
- Circulatory changes
- Renal failure
- Clearance
- Fluid balance
- Organ support
- Hepatic dysfunction
- Race
- Renal failure
- Clearance
- Fluid balance
- Organ support
- Hepatic dysfunction
Current approach to drug monitoring

Laboratory → Checked in → Spun → Analysed → Reported

Dose adjustment → Interpreted → Reviewed by prescriber
Can technology improve the way we dose antibiotics?

Closed-loop control for precision antimicrobial delivery.
Already validated in diabetes control through individualised insulin delivery and anaesthesia control intra-operatively

Improved methods for drug monitoring required

Minimally invasive
Point-of-care
Continuous monitoring
Broad range of agents
Electrochemical Biosensors

Currently described:
- Penicillin
- Aminoglycosides
- Macrolides
- Quinolones
- Tetracyclines
- Rifampicin
- Metronidazole
- Lincomycin
- Sulphonamides
- Chloramphenicol
- Voriconazole
Aptamer biosensors

- Single stranded DNA or RNA sequences
- Bind to specific target molecules
- Selected by *systematic evolution of ligands by exponential enrichment* (SELEX)
Invasive drug monitoring

- Aptamer biosensor
- Central venous insertion
- Monitor in ambulatory animals
- Challenges:
  - Acceptability outside of ICU
  - Venous thrombosis
  - Bleeding

Figures from Arroyo-Currás et al, PNAS; 2017

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Minimally invasive monitoring

Interstitial Fluid (ISF) is in equilibrium with capillary blood.

Composition includes:
Metabolites, drugs, and proteins.
Microneedle based sensing

Hydrogel
Tissue Compatibility

Gold
IrOx (pH Sensing)

β-lactamase

Penicillin

Penicillinoic acid
& Proton

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In-vivo monitoring

In-vivo results during penicillin-V dosing

- Penicillin sensor
- Control sensor

Potential vs. Ag/AgCl [V]

- Penicillin V 500mg PO

Time (hrs)

Rawson, et al, 2018
Closed-loop control

A closed-loop control system for precision antimicrobial delivery

Define PK-PD target  Variation in CL  Sensor error

Rawson, O’Hare, et al. JAC; 2018; Herrero, Rawson, et al. TBME; 2017; Phillip, Rawson, et al; JHI (Supp 1); 2016
Closed-loop control

Continuous infusions – PID controller

\[ \text{PID Controller Output} = K_p \cdot \text{Error} + K_d \cdot \frac{d\text{Error}}{dt} + K_i \cdot \int \text{Error} \]

Intermittent infusions – ILC controller

\[ ILC \text{ Output} = U_k(t) = U_k(t) + \gamma e_k(t + 1) \]

Rawson, O’Hare, et al. JAC; 2018; Herrero, Rawson, et al. TBME; 2017; Phillip, Rawson, et al; JHI (Supp 1); 2016
PK-PD targets for therapy

**MIC gold standard**
- *In-vitro*, static measure
- Ignores host factors

Use in empirical therapy?

Link with rapid diagnostics?

**Are there alternatives / adjuncts?**
- Kill curves
- AUC:EC$_{50}$

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Mueller et al, AAC 2004; Ramos-Martin et al, JAC 2016; Rawson et al, TDM 2018
Can CRP predict vancomycin PD?

Vancomycin PK
\[ \frac{dX(1)}{dt} = R(1) + X(2) \cdot Kpc - X(1) \cdot \left( \frac{SCL}{V} \right) - X(1) \cdot Kcp \]
\[ \frac{dX(2)}{dt} = X(1) \cdot Kcp - X(2) \cdot Kpc \]

C-reactive protein
\[ \frac{dX(3)}{dt} = (KCRPp \cdot X(3) \cdot \left( \frac{1}{P0Pmax} \right) - \left( \frac{KCRPi \cdot X(3) \cdot \left( \frac{X(1)}{V} \right)^n}{EC50^p \cdot \left( \frac{X(1)}{V} \right)^n} \) \]

- Potential to provide *in-vivo* host and organism response data.
- May be useful adjunct to MIC
- Role during empirical phase for truly individualised therapy?
- Role of other markers, such as procalcitonin?
Intelligent use of data

**Patient level data**
- Individual rich PK data from biosensors
- Individual patient electronic health records
- Individual patient microbiology records

**Pooled data**
- Pooling of data centrally with biobank data

**Analytics**
- Application of machine / supervised machine learning
- Population PK modelling

**Informing practice**
- Individualised dosing recommendations
- Extrapolation to settings with limited supporting evidence
- Holistic understanding of appropriate therapy

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Integrated platforms

Requirements
- Low cost
- Low power
- Ease of use
- Integrated with other CDSS
- Low maintenance
- Reliable / Valid

Deliverables
- Dynamic dosing
- Multiple compartments
- Minimally invasive
- Missing gap in “appropriateness”
- Targeted agents

Integrated dose optimization platforms
Summary

• (Dynamic) dose optimization important consideration of appropriate antimicrobial therapy.

• Current approaches have a number of problems.

• Technology offers a new frontier to improve antimicrobial drug monitoring.

• Development must focus on acceptability across care settings.