Barnett Christie Lecture 2017

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NIHR invention for innovation (i4i) Clinical Research Fellow
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@TmRawson
What is the role of artificial intelligence and biosensors in achieving individualised antimicrobial therapy?
Background project

Integrated clinical decision support tools for antimicrobial management

- Personalised antimicrobial selection
- Precision dosing
- Patient engagement

Diagnostics & Surveillance

Delivered at point of care
Within end-user workflow
Clinical decision support systems

Increased reporting of clinical decision support systems

Current systems

Rules based systems.
Narrow focus on antimicrobial selection.
Few utilise developments in informatics.
Identified gaps with decision support

Greater need for flexibility in the face of inter-individual variation

Gaps in:
- Dose optimisation
- Physician engagement with AMS programmes
- Patient engagement
- Ability to integrate with novel diagnostics

Failures in adoption of interventions

Understanding physicians decision making pathways

Rawson, Moore, et al. Clinical Microbiology and Infection. 2017
Rawson, Tivey, et al. Antimicrobial Resistance and Infection Control 2017
The gap is also reflected in education

Primary care:
• Prescribes 74% of antimicrobials
• Has 2/1368 unique learning points on AMS – AMR in total

Overall, only 40% of points require demonstration of a behaviour
Provide better and more individualised data at each step of the physicians decision making pathway to promote better decisions.

Rawson, Charani, et al. BMC Medicine; 2017
Artificial intelligence

Concept of marrying computer algorithms with statistics.

Free from limitations of human thinking it allows the machine to be able to identify patterns that are buried within data.

Facilitates learning.
Antibiotic selection

Case based reasoning (CBR)
Solves a new problem by remembering previous similar situations and reusing knowledge and data to inform recommendations.

Presentation with possible infection

Physician entry

Trust servers

New Case

45 parameters

Past Cases

Treatment Recommendation

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Hernandez, Herrero, Rawson, et al HEALTHINF; 2016
Rawson, Thesis 2017
Case based reasoning

Intensive care
CBR vs. expert opinion.
High level of agreement.

Non-critical care
CBR vs. susceptibility data.
High concordance.
Reduced spectrum.

Lactate drives decisions

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Hernandez, Herrero, Rawson, et al HEALTHINF; 2016
Rawson, Thesis 2017
Predicting positive microbiology

Presentation with possible infection

Using WCC, CRP, Cr, ALT, ALP, and Bilirubin.

Microbiology  Blood Sciences

Supervised machine learning

Likelihood estimate

Support Vector Machine (SVM)

ROC: 0.88
Predicting positive blood culture

Predicting bacteraemia

- ROC: 0.74 (95% CI: 0.66-0.88)

- Mean probability:
  - 0.82 - BSI
  - 0.51 - Control

* Significant difference in distributions observed, p<0.01

Distribution of probability scores
Next stages

Exploring other aspects of prescribing that AI can support.

Protocols for system curation and oversight.

Embedding tools into end-users workflow.

Ensuring systems are agnostic to different healthcare systems.

Integration with other aspects of decision support.
Dose optimisation

![Bar chart showing variation in vancomycin therapy in obesity](chart)

- **Amoxicillin (T = 50%)**
- **Augmentin (T = 100%)**
- **Piperacillin (T = 50%)**
- **Flucloxacillin (T = 50%)**
- **Ceftriaxone (T = 100%)**

Key:
- T = Time
- 100% = Trough
- 50% = Mid-dosing interval

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Dosing is a dynamic process

**Inter-individual variability**
- Age
- Race
- Ethnicity
- Gender
- Comorbidities
- Medications

**Intra-individual variability**
- Hyper-dynamic circulation
- Altered fluid balance
- Renal dysfunction
- Hepatic dysfunction
- Augmented renal clearance
- Organ support

Rawson, O’Hare, et al. Journal of Antimicrobial Chemotherapy; 2017
Individualised dosing

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
Minimally invasive sensing

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

Composition includes:
Metabolites, drugs, and proteins.
Bio-inspired β-lactam sensor

- Penicilllin
- Penicillinoic acid & Proton

Hydrogel Tissue Compatibility

- Gold IrOx (pH Sensing)
- β-lactamase

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Laboratory characterisation

Calibrated in artificial interstitial fluid for penicillin-G, amoxicillin, ceftriaxone, and imipenem.
Laboratory characterisation

Physiologically inspired calibration rig

pH calibration of microneedles

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Human testing – penicillin V

Applied to non-dominant forearm
Semi-portable potentiostat connected
Recording once every second
Worn for 6 hours
Human testing – penicillin V

Response to penicillin bolus observed
Resolution of skin changes within 12 hours of use

With thanks to S. Gowers
Enzyme based biosensors

- Gold
- IrOx (pH Sensing)
- β-lactamase
- Hydrogel
- Tissue Compatibility

Penicillin
Penicillinoic acid & Proton
# Antibiotic electrochemical sensors

## Analyte (substrate)
- Biological detection
  - Enzyme
  - Aptamer
  - Antibody
  - Chemoreceptor
- Transducer
- Signal
- Signal processing

## Described antimicrobial biosensors
- Penicillin
- Aminoglycosides
- Macrolides
- Quinolones
- Tetracyclines
- Rifampicin
- Metronidazole
- Lincomycin
- Sulphonamides
- Chloramphenicol

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Aptamer based sensing

Far = Low Current
Near = High Current

Tetracycline Sensing

SWV derived peak current of a Kanamycin Aptasensor in Clean Buffer

Tetracycline Sensing

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Closing the loop

A closed-loop control system for precision antimicrobial delivery

Define PK-PD target

Variation in CL

Sensor error

Rawson, O’Hare, et al. Journal of Antimicrobial Chemotherapy; 2017
Herrero, Rawson, et al. Transactions on Biomedical Engineering; 2017 [IN PRESS]
Phillip, Rawson, et al; Journal of Hospital Infection (Supp 1); 2016
Closed loop control systems

A closed-loop control system for precision antimicrobial delivery

Continuous infusions – PID controller

Intermittent infusions – ILC controller

Rawson, O’Hare, et al. Journal of Antimicrobial Chemotherapy; 2017
Herrero, Rawson, et al. Transactions on Biomedical Engineering; 2017 [IN PRESS]
Phillip, Rawson, et al; Journal of Hospital Infection (Supp 1); 2016
Next phases of development

- Clinical validation of continuous monitoring in humans.
- Expanding the number of agents.
- Integration of clinical biomarker sensing.
- Pooling of data to form databank.
- Point-of-care monitoring devices.
In conclusion

What is the role of artificial intelligence and biosensors in achieving individualised antimicrobial therapy?

A new frontier in individualised management of infections.

Artificial intelligence provides ability to utilise routinely available data.

Minimally invasive biosensor technology provides a novel way of performing drug monitoring.

Closed-loop control can facilitate individualised dosing of antimicrobials.
Acknowledgements