A Point-of-care, Informatics- based Randomised, controlled trial for decreasing overutilisation of Antibiotic ThErapy

Dr. Angela Huttner (Principal Investigator), Dr. Angèle Gayet-Ageron, Prof. Stephan Harbarth, Prof. Laurent Kaiser, Dr. Virginie Prendki, Dr. Rodolphe Meyer, Dr. Anne Rossel, Dr. Elodie von Dach

Prof. Pierre-Yves Bochud (site PI), Ms. Aurélie Barbet, Dr. Anne-Sophie Brunel, Ms. Corine Guyaz

Dr. Werner Albrich (site PI), Dr. Domenica Flury, Ms. Cornelia Knapp, Ms. Simone Kessler, Dr. Eva Lemmenmeier

CHALLENGES & GOALS

- Our best intentions for the patients of today may be harming the patients of tomorrow. Physicians in Switzerland are cognizant of the current level of resource waste, but are confronted daily by an unfortunate triad: sick individuals in need of immediate help, a relative wealth of diagnostic and therapeutic options, and only a meagre evidence base proving that many of these options are unnecessary for the patient at hand.
- **New methods to strengthen this evidence base—efficiently and at low cost—are long overdue.**
- Clinical evidence is ubiquitous, present in every patient's outcome after any intervention. But our current model for collecting it is expensive and inefficient.
- Randomised controlled trials (RCTs), our most methodologically robust tool, remain the gold standard (Figure 1).[1]
- But traditional RCTs are costly, time-consuming, and exclusive: elderly and the chronically ill, who represent the majority of hospitalised patients in Switzerland, are frequently excluded.
- Meanwhile, in the clinic, spontaneous "pseudo-randomisations" continue to occur every day; healthcare providers' decisions are often based on arbitrary and individual preferences, local dogma, or anecdotal experiences. **This abundance of clinical experience goes uncollected and unexamined.**
- **The PIRATE project is the first point-of-care randomisation trial in Switzerland**; it leverages the electronic health record (EHR) to identify, randomise and gather pertinent outcomes data from patients with Gram-negative bacteraemia, a frequent and serious infection in comorbid and elderly patients.

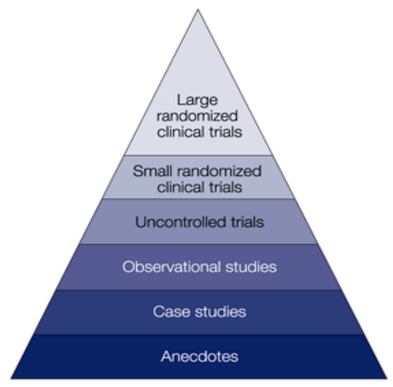

Figure 1 - Hierarchy of clinical evidence.[1]

RESEARCH QUESTIONS & METHODOLOGY

Patients with chronic illnesses rely most on antibiotics and, through no fault of their own, misuse them the most.[2,3] Prolonged antibiotic courses result in unnecessarily long hospital stays and, on a larger level, drive the increases we are witnessing globally in antibiotic resistance.[4]

Antibiotics are a limited resource without which these individuals cannot safely undergo routine cardiovascular and joint-replacement surgeries, chemo- and other immunosuppressive therapy, and for whom common infections and minor injuries could once again become life-threatening.[5]

No RCT evaluating the optimal duration of therapy for Gram-negative bacteraemia (GNB) has been published. Traditionally, guidelines have somewhat arbitrarily recommended long antibiotic courses of two weeks, even though patients with no structural complications may recover after only five days of therapy.[6] Direct evidence is mounting that longer antibiotic courses leave patients at risk of acquiring difficult-to-treat multi-resistant organisms.[7]

A classic randomised controlled trial…

The PIRATE project is a multicentre, point-of-care randomised trial whose purpose is to prove the non-inferiority of shorter (7 days) or individualised (C-reactive protein-guided) durations to the traditionally longer 14-day course. Figure 2 depicts the trial's overall design and flow.

With a modern, bio-informatics-based twist:

Figure 3 demonstrates the work that HUG bio-informatics specialists are conducting to automate much of the work inherent to a multicentre randomised trial. **The hospital's electronic health record**:

- Automatically **identifies eligible patients** using the inclusion-criteria-derived variables *age*, *blood-culture results* (Gram-negative bacteria), and *antibiotic therapy*
- can **perform the randomisation** to one of the three study arms
- **automatically populates the study's electronic database** (Secutrial®) with follow-up clinical and microbiologic outcomes data via nightly data transfers, thereby greatly decreasing workload and risk of transcription errors

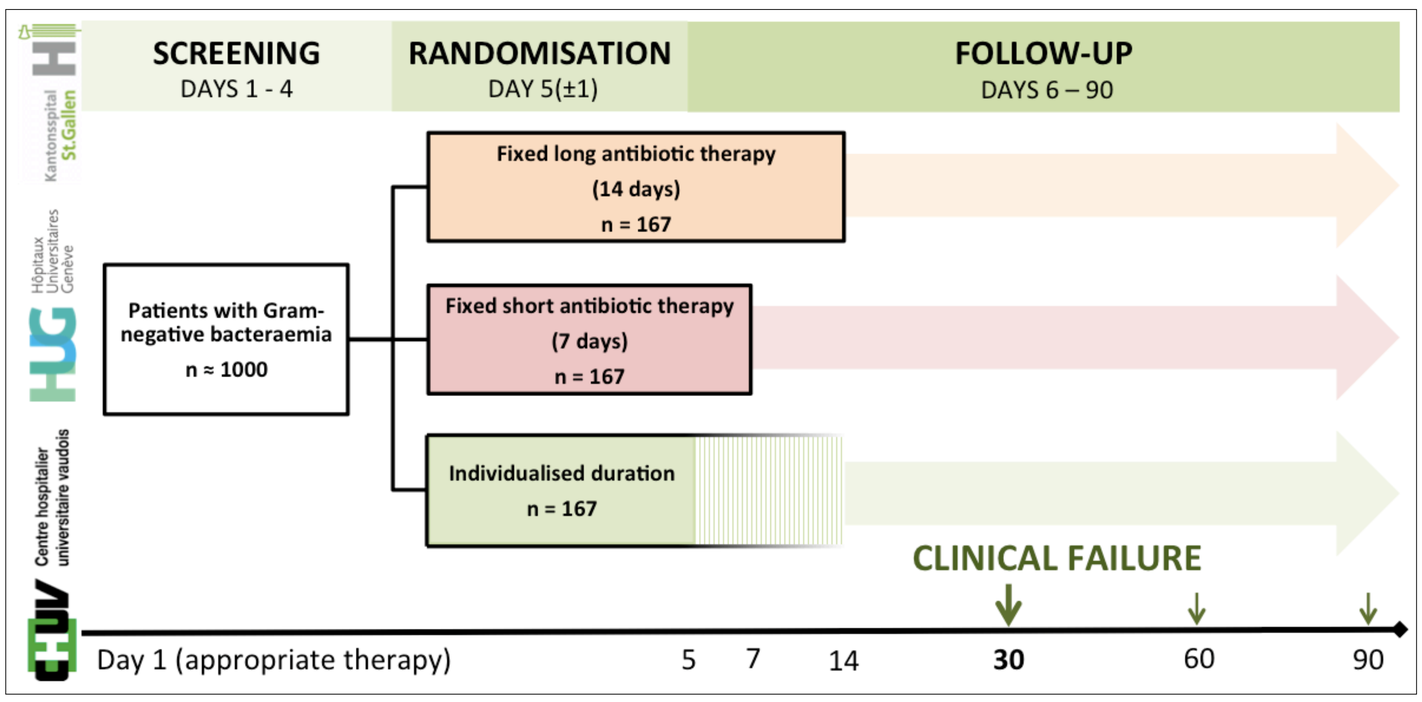

Figure 2 - Trial flow. Day 1 is defined as the first day of microbiologically appropriate antibiotic therapy. Patients are randomised on day 5 (±1) and followed until day 90.

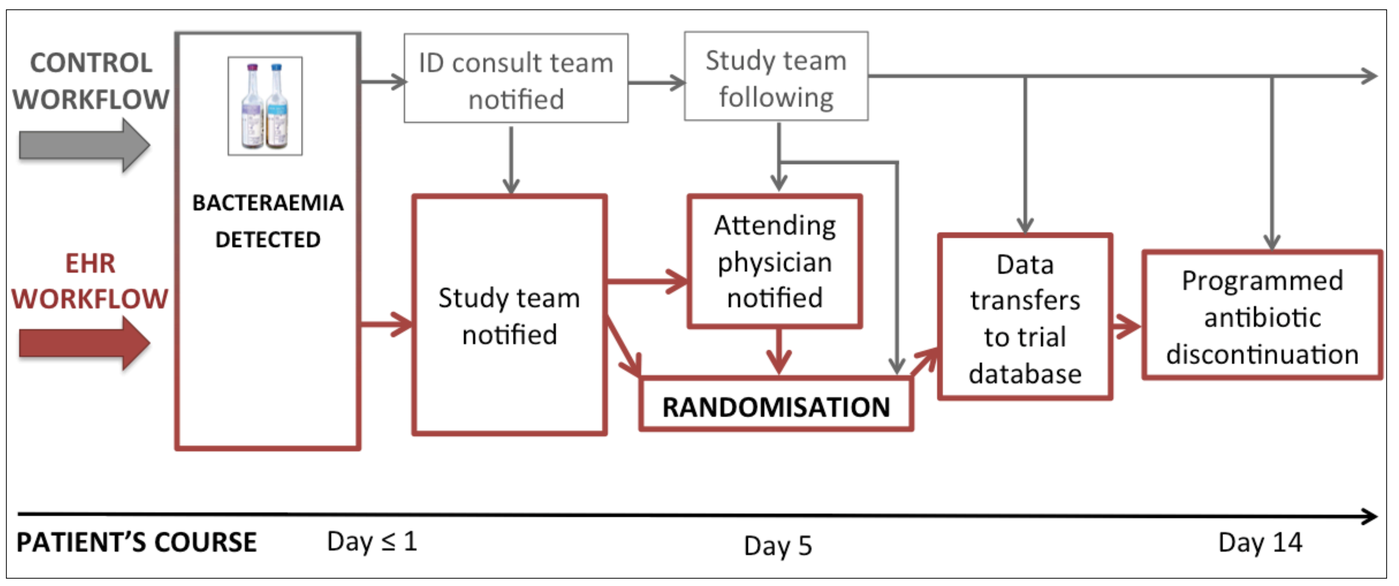

Figure 3 - Electronic-healthcare record workflow for patient identification, randomisation and follow-up. The EHR workflow is outlined in red, the control ("back-up") workflow in grey. Grey arrows indicate safety valves; these cover all points at which the EHR workflow could malfunction. In this hypothetical case, the patient has been randomized to the control arm (antibiotic therapy duration of 14 days).

EXPECTED RESULTS, IMPACT

- Non-inferiority of shorter and individualised antibiotic durations is strongly anticipated given this trial's prudent design, with inclusion of patients who have already stabilized clinically after initiation of appropriate antibiotic therapy.
- Thus most immediately, unnecessary antibiotic use can be safely and significantly reduced: physicians in Switzerland and abroad will have the evidence from a RCT that they currently lack, and antibiotic consumption due to this frequent infection will, in many cases, be halved. A further direct benefit will be the prevention of a significant number of multidrug-resistant infections.
- The point-of-care trial platform established via the PIRATE project can be repurposed to study myriad other clinical scenarios where equipoise among treatment approaches is abundant, but properly collected evidence is not. This includes settings ranging from outpatient clinics to intensive-care units, and interventions ranging from specialized therapy to population-level preventive measures
- Through systematic and rigorous evaluation of the clinical outcomes of tested interventions, the POC platform will identify strengths and weaknesses in current healthcare delivery and guide clinicians and public-health officials towards a more evidence-based and judicious use of resources.

REFERENCES

1 – Engel LW, Straus SE. *Nat Rev Drug Discov* 2002; **1**(3): 229-37).
2- Fleming A, Bradley C, Cullinan S, Byrne S. *Drugs Aging.* 2015;32(4):295-303.
3- Loeb M, Simor AE, Landry L, et al. *J Gen Intern Med.* 2001;16(6):376-383.
4- Shorr AF, Micek ST, Welch EC, Doherty JA, Reichley RM, Kollef MH. *Crit Care Med.* 2011;39(1):46-51.
5- Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R.. *Lancet Infect Dis.* 2015;15(12):1429-1437.
6- Havey TC, Fowler RA, Daneman N. *Crit Care.* 2011;15(6):R267.
7- Chastre J, Wolff M, Fagon JY, et al. *JAMA.* 2003;290(19):2588-2598.

FNSNF Swiss National Science Foundation
74 NRP Smarter Health Care National Research Programme