The PIRATE PROJECT: a Point-of-care, Informatics-based Randomized, controlled trial for decreasing over-utilization of Antibiotic Therapy in Gram-negative Bacteremia

Dr. Angela Huttner, FMH
Division of Infectious Diseases
Geneva University Hospitals
5 December 2017

angela.huttner@hcuge.ch
Outline

• Finding the evidence to support a reduction in antimicrobial usage
  – Point-of-care (POC) randomization trials
    • Learning healthcare systems

• The PIRATE project
  – Antibiotic resistance & what we should learn from our patients
  – Randomization at the point of care for determining optimal antibiotic durations for Gram-negative bacteremia
  – Substudies
When the drugs don’t work because we overused them because we lacked evidence to show that less usage is OK.
Point-of-care randomization studies

- Hierarchy of evidence

- We don’t have enough randomized controlled trials in infectious diseases (only 16% of IDSA recommendations based on them)

- And even randomized controlled trials may lack external validity...

- Spontaneous randomizations occur daily in the clinic, but this “evidence” goes uncollected (anecdotes)


Point-of-care randomization studies

- Use the electronic health record (EHR) to structure spontaneous “pseudo-randomizations” at the point of care
- Enable the coherent study of patient outcomes
  - Data from “real” patients
  - Follow-up visits integrated into usual care
- Clinical evidence can come only from the clinic
- Only suitable for comparing approved treatments or diagnostic techniques toward which there is clinical equipoise

Fiore et al. Clin Trials 2011;8(2):183-95
A learning healthcare system is...designed to generate and apply the best evidence for the collaborative healthcare choices of each patient and provider; to drive the process of discovery as a natural outgrowth of patient care; and to ensure innovation, quality, safety, and value in health care.
1. Respect the rights and dignity of patients
2. Respect the clinical judgments of clinicians
3. Provide optimal care to each patient
4. Avoid imposing nonclinical risks and burdens on patients
5. Reduce health inequalities among populations
6. Conduct activities that foster learning from clinical care and clinical information
7. Contribute to the common purpose of improving the quality and value of clinical care and health care systems

Point-of-care randomization

- How the randomization actually works:

  **Minimal EHR involvement:**
  Doctor receives a small alert from the EHR that patient could be eligible for the trial.

  **Strong EHR involvement:**
  With study team approval, the electronic health record performs the randomization.
Box 2
Hypothetical examples of point-of-care trials in infectious disease

- Duration studies: optimal duration of antibiotic therapy for (a) community-acquired pneumonia, (b) uncomplicated pyelonephritis, (c) Gram-negative bacteraemia; early switch to oral antibiotic therapy; etc.
- Antibiotic choice studies: linezolid vs. vancomycin for skin and soft tissue infections; fosfomycin vs. ciprofloxacin for prophylaxis before transrectal prostate biopsy; cloxacillin vs. cefazolin for MSSA bacteraemia; combination vs. monotherapy for carbapenem-resistant, Gram-negative infections; β-lactam monotherapy vs. β-lactam/aminoglycoside for Pseudomonas aeruginosa bacteraemia; etc.
- Dosing and schedule: meropenem 1 g three times a day vs. 2 g three times a day; intermittent vs. continuous infusion of antibiotics; pharmacokinetic studies in which no more than routine blood sampling is needed; etc.

MSSA, methicillin-susceptible Staphylococcus aureus.
Establishing a point-of-care randomization platform in Switzerland

• Help from above

• A convincing & “easy” first test case, with plenty of safety valves...

Study question of the platform’s prototype trial:
Are shorter antibiotic courses non-inferior to 14 day courses for Gram-negative bacteremia?
Rationale for the PIRATE project

• We know we overuse antibiotics
• We know that this overuse leaves patients with resistant organisms
• Antibiotic durations are arbitrary…and lunar!
• But physicians are generally afraid to shorten durations without solid (randomized) evidence

Are shorter antibiotic courses non-inferior to 14 day courses for Gram-negative bacteremia?

- **Gram-negative bacteremia is on the rise**
  - Patients are getting older, more co-morbid, and more immunosuppressed

- No RCT evaluating the optimal duration of therapy for Gram-negative bacteremia (GNB) has been published

- Some physicians give 14 days of antibiotics, some 7...and some even only 5 (“pseudo-randomizations”)

- Indirect evidence that, in patients without structural complications who are improving, shorter durations are safe

References:

Rationale for the PIRATE project

• So why not structure these pseudo-randomizations at the point of care and follow our patients’ clinical outcomes?
The PIRATE trial’s sites...
 … and team

Laurent Kaiser  Stephan Harbarth  Anne Rossel

Thomas Perneger  Angèle Gayet-Agéron  Elodie von Dach  Angela Huttner

Pierre-Yves Bochud

Werner Albrich
Study design

Randomized (1:1:1) controlled, triple-blind phase IV POC trial

= 500 patients

Designated investigators & patients blinded until antibiotic discontinuation
Analyst blinded
Population, outcomes

**Inclusion criteria:**
1. Age $\geq$ 18 years
2. The presence of Gram-negative bacteria in at least one blood culture bottle
3. Treatment with a microbiologically efficacious antibiotic

**Exclusion criteria:**
1. Immunosuppression
2. Abscess/ other complications
3. Certain “difficult” organisms
4. Etc....

Primary outcome = clinical failure = at least one of the following:

- **Relapse:** a recurrent bacteremia due to the same bacterium occurring from the day of treatment cessation through day 30
- **Local suppurative complication** not present at infection onset
- **Distant complications** of the initial infection, defined by growth of the same bacterium causing the initial bacteremia (as determined by antibiotic susceptibility profiling)
- **The restarting of Gram-negative-directed antibiotic therapy** due to clinical worsening suspected to be due to the initial infecting organism and for which there is no alternate diagnosis/pathogen suspected
- **Death** due to any cause through day 30
**Electronic-healthcare record workflow for patient identification, randomization 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).
### Study schedule (keeping it simple)

<table>
<thead>
<tr>
<th>Study visit/observation point</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timeline (days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Window period (days)</td>
<td>0-4</td>
<td>5</td>
<td>±2</td>
<td>±2</td>
<td>±7</td>
<td>±14</td>
<td>±21</td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP measurement* (2ml blood)</td>
<td></td>
<td>(X)</td>
<td>(X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs reviewed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>SAEs reviewed</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other outcomes data collected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Notes:*
- CRP: C-reactive protein
- AEs: Adverse Events
- SAEs: Serious Adverse Events
# Study timeline

**Geneva** launch 1 April 2017

**Lausanne & St. Gallen** launch 1 May 2017

## Milestones

<table>
<thead>
<tr>
<th>Preparation phase</th>
<th>Study period</th>
<th>Study close-out</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year 1</strong></td>
<td><strong>Year 2</strong></td>
<td><strong>Year 3</strong></td>
</tr>
<tr>
<td>Q1 Jan - Mar 2017</td>
<td>Q1 Jan - Mar 2018</td>
<td>Q1 Jan - Mar 2019</td>
</tr>
<tr>
<td>Q2 Apr - Jun</td>
<td>Q2 Apr - Jun</td>
<td>Q2 Apr - Jun</td>
</tr>
<tr>
<td>Q3 Jul - Sept</td>
<td>Q3 Jul - Sept</td>
<td>Q3 Jul - Sept</td>
</tr>
<tr>
<td>Q4 Oct - Dec</td>
<td>Q4 Oct - Dec</td>
<td>Q4 Oct - Dec</td>
</tr>
</tbody>
</table>

- Protocol development
- Contracts signed
- Ethics committee approvals
- Study dissemination, outreach
- Data management (EHR, eCRF)
- Patient recruitment
- Site monitoring
- Interim analysis
- Database cleaning, exports
- Database lock & analyses
- Manuscript preparation
- Publication, dissemination

## Two-year recruitment period
5 – The safety valves: extensive investigator documentation of the initial encounter and self-monitoring with post-consent follow-up and mandatory reporting to the ethics committee
The obvious concern with the general information model is that it could represent a “slippery slope.” If patients are not required to sign an informed consent form, investigators may be tempted to act paternalistically, assuming the patient’s consent in most cases and subsequently cutting the corners so painstakingly established by the Geneva Conventions and later the Belmont Report and the Declaration of Helsinki.

For this reason we propose (1) a strict level of documentation by study investigators recording the initial encounter (time and place of occurrence, persons present, time required to present and explain the study and time needed by patient to decide on participation) and (2) self-monitoring of post-consent follow-up with required, regular reporting of results to the ethics committee. The monitoring will proceed as follows:

- All initially consenting patients will be re-contacted
  - Within two weeks following enrollment (± 5 days)
  - At days 30, 60 and 90
- And will be asked
  - Whether they remember consenting to participate in the trial
  - Whether they have specific questions pertaining to the trial

The results will be documented and sent to the principal investigator for compiling. They will then be sent bi-annually (four times over the two-year recruiting period) to the ethics committee. They will also be monitored regularly by the study’s external monitor. Finally, the results will be compared to those of historical controls such as those published by Chenaud et al. and published for the benefit of the clinical and bioethics communities (see secondary outcomes).
<table>
<thead>
<tr>
<th>Remarques générales</th>
<th>We thank the Commission for this kind assessment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nous vous félicitons pour ce projet qui sort du lot autant pour le fond que pour la forme</td>
<td></td>
</tr>
</tbody>
</table>

| Ecrans 1-3 (correspond à l’ancien formulaire de base)                                |                                               |
|------------------------------------------------------------------------------------|                                               |
| 1. A l’écran 2, est-il justifié de dire que votre étude est « double-blind » ?      | We agree; we have removed this description from the form. |

<p>| Formulaire d’information                                                            |                                               |
|------------------------------------------------------------------------------------|                                               |
| 2. Nous encourageons les efforts qui visent à améliorer le processus de consentement, mais en l’état, le degré de simplification n’est pas évident car il s’agit en fait simplement de donner un formulaire d’information ordinaire puis de documenter leur consentement dans une note de suite plutôt que de leur demander de signer le document usuel. En soi ce n’est pas une mauvaise idée, mais il y a deux hics : |                                               |
| • La loi suisse requiert la forme écrite pour le consentement à la recherche. Ce point est abordé dans le commentaire ci-dessous, et la solution de faire signer un témoin est effectivement réalisable. Elle aurait l’avantage de faire intervenir une tierce personne susceptible d’aider le participant potentiel à prendre sa décision, mais l’inconvénient qu’il faudrait à chaque fois trouver une telle personne, qui ne peut être affiliée à l’étude. |                                               |
| • We understand and have amended the protocol and informed consent to allow for a witness unrelated to the study to sign the consent form once the patient has been fully informed and has consented. | Protocol v1.1 p.33, Section 8.3, and p.28, Section 6.1 |</p>
<table>
<thead>
<tr>
<th><strong>Ethics Commission’s response</strong>...</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• On distingue le formulaire d’information du formulaire de consentement. Or, ce dernier a un contenu, qui est perdu ici. Il faudrait le cas échéant importer ce contenu dans le formulaire d’information.</strong></td>
</tr>
<tr>
<td><strong>Auriez-vous la possibilité de comparer les diverses formes de consentement (taux d’acceptation, compréhension etc.) à l’intérieur de votre protocole et de nous soumettre une proposition ? Des questionnaires standardisés existent déjà (contacter <a href="mailto:samia.hurst@unige.ch">samia.hurst@unige.ch</a> pour plus de renseignements si nécessaire)</strong></td>
</tr>
<tr>
<td><strong>3. Document « streamlined ic » justifiant l’obtention du consentement oral des participants :</strong></td>
</tr>
<tr>
<td>Selon l’OClin, les seules exceptions à la forme écrite du consentement sont les suivantes:</td>
</tr>
<tr>
<td>a. lorsque, pour des raisons corporelles ou cognitives, la personne concernée ne peut pas lire ou écrire; et</td>
</tr>
<tr>
<td>b. lorsque l’investigateur apporte la preuve de l’information et du consentement, notamment par le biais d’une attestation écrite de témoins ou de l’enregistrement du consentement donné verbalement.</td>
</tr>
<tr>
<td>Nous vous recommandons d’opter soit pour l’attestation écrite du témoin soit pour l’enregistrement du consentement donné par le patient à l’oral (OClin art.8 al.1b).</td>
</tr>
<tr>
<td><strong>• We have now added the consent form to the information brochure.</strong></td>
</tr>
<tr>
<td><strong>• We have now included in the study protocol the proposal, previously described in Appendix 1, to compare the different forms of consent. This is now described, with more methodologic detail, as a nested, prospective observational cohort study.</strong></td>
</tr>
<tr>
<td><strong>We have amended the protocol and informed consent to allow for a witness unrelated to the study to sign the consent form once the patient has been fully informed and has consented.</strong></td>
</tr>
<tr>
<td><strong>Protocol v1.1</strong></td>
</tr>
<tr>
<td><strong>p. p.28, Section 6.1</strong></td>
</tr>
<tr>
<td><strong>Protocol v1.1</strong></td>
</tr>
<tr>
<td><strong>p.33, Section 8.3, and p.28, Section 6.1</strong></td>
</tr>
</tbody>
</table>
Written vs. oral consent: a substudy!

**Informed Consent (follow-up)**

1. Does the patient remember that he/she is participating in this study?  
   - [ ] yes  
   - [ ] no
2. Does the patient remember that he/she granted consent to participate?  
   - [ ] yes  
   - [ ] no
3. Does the patient remember the purpose of the study?  
   - [ ] yes  
   - [ ] no
4. Does the patient remember the risks of the study (as described at enrollment)?  
   - [ ] yes  
   - [ ] no
5. Does the patient have questions now related to the study?  
   - [ ] yes  
   - [ ] no

Signed by

Reason

Project version
About that external validity...

• How representative are our included patients?

• EPCO: Excluded patients’ outcomes
  – Prospective observational study examining PIRATE’s primary outcome in those we didn’t enroll
The study that still needs to be done

- Metagenomic analysis of the microbiota in patients who had shorter versus longer antibiotic courses:

  Will we indeed decrease the number of antibiotic resistance genes (ARG) that we carry (and transmit)?
Comments, questions?

Thank you