Antibiotics
How Long Do We Need to Treat?

Rob Fowler
Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto

Nick Daneman
Division of Infectious Diseases, Sunnybrook Hospital, University of Toronto
Disclosure

There are only two things we don’t know about Infectious Diseases in the ICU…
There are only two things we don’t know about Infectious Diseases in the ICU…*

1. Which antibiotic to use

2. How long to use it
Make sure you finish all these pills. Even if you are feeling better.
We’re going to tuck you in for the weekend with a cozy blanket of Vancomycin and Piperacillin-Tazobactam
We don’t want to treat for too short

- Clinical failure
- Relapse
- Selecting resistance in culprit pathogen
We don’t want to treat for too long

• Selecting resistance

• *C. difficile*

• Other antibiotic adverse events

• Costs
Antibiotic Resistance is Rising: MRSA BSI

National MRSA-BSI infection rates, 1995 to 2014
Antibiotic Resistance is Rising: VRE

Incidence rates of vancomycin-resistant Enterococcus infections per 1,000 patient admissions and per 10,000 patient days
Antibiotic supply is diminishing

The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.

*Intervals from 1980–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents. Data courtesy of FDA's Center for Drug Evaluation and Research (CDER).
Antibiotics are not Innocuous

- Estimated 140,000 ER visits per year in U.S. due to antibiotic allergy, adverse events

- Among hospitalized patients treated with antibiotics
  - 8% experienced an adverse event
    - 40% of these were serious adverse events

Gholami *Pharma Drug Safety* 2005; Shehab *CID* 2007
Rates of Clostridium difficile Infection Among Hospitalized Patients Aged ≥65 Years,* by Age Group --- National Hospital Discharge Survey, United States, 1996--2009
Antibiotics Cost a Lot

- Canada – $20,000/1000 inhabitants
  – ~$600 million in outpatient antibiotics alone

Figure 37. Total number of prescriptions and total cost per 1,000 inhabitants for oral antimicrobials dispensed by retail pharmacies in Canada, 2000–2008.
Much of Antibiotic Use is Inappropriate

• 30-50% of antibiotic use is unnecessary or inappropriate

• Greatest contributor is excessive treatment length

Hecker Arch IM 2003
Why Focus on Treatment Duration to Reduce Antibiotic Overuse?

• It’s difficult to minimize antibiotic *initiation*
  
  • Diagnoses not always clear
  
  • Microbiologic test results can be delayed, falsely negative
  
  • Early adequate antibiotic coverage strongly associated with survival
Early Antibiotics Save Lives

Feature Articles

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

Crit Care Med 2006 Vol. 34, No. 6
Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%.
Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%.

- Antibiotics within 1 hour of hypotension – 80% survival
- Each hour of delay decreased absolute survival by 8%
Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%.

- Time to effective antimicrobial the single strongest predictor of outcome.
- Median time to antibiotics ~ 6 hrs!
Why Focus on Treatment Duration to Reduce Antibiotic overuse?

• It may be easier to reduce *lengths* of treatment courses

  – Diagnosis *clearer* as time goes by
  – Microbiology *results* become available
  – *Clinical course* of patient evident
  – Treatment beyond cure exposes patient to harms without benefit
Evidence Piling Up that Short Duration Treatment Is Sufficient: VAP

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults
A Randomized Trial

Probability of survival is for the 60 days after ventilator-assisted pneumonia onset as a function of the duration of antibiotic administration.
Evidence Piling Up that Short Duration Treatment Is Sufficient

**Figure 2.** Kaplan-Meier Estimates of the Probability of Survival

Powered to allow up to a **10% Non-inferiority Margin**

Comparison of Antibiotic Therapy for Pneumonia in Adults
A Randomized Trial

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Days After Bronchoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8-Day Antibiotic Regimen</td>
</tr>
<tr>
<td></td>
<td>15-Day Antibiotic Regimen</td>
</tr>
</tbody>
</table>

Probability of survival is for the 60 days after ventilator-assisted pneumonia onset as a function of the duration of antibiotic administration.

Chastre *JAMA* 2003
Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

# Short Course Antibiotics for Intra-abdominal Infection

## Comparison of Treatment Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (N = 260)</th>
<th>Experimental Group (N = 257)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>58 (22.3)</td>
<td>56 (21.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>Surgical-site infection</td>
<td>23 (8.8)</td>
<td>17 (6.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Recurrent intraabdominal infection</td>
<td>36 (13.8)</td>
<td>40 (15.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.8)</td>
<td>3 (1.2)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

## Time to Event — No. of Days After Index Source-Control Procedure

<table>
<thead>
<tr>
<th>Event</th>
<th>Control Group</th>
<th>Experimental Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of surgical-site infection</td>
<td>15.1±0.6</td>
<td>8.8±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis of recurrent intraabdominal infection</td>
<td>15.1±0.5</td>
<td>10.8±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>19.0±1.0</td>
<td>18.5±0.5</td>
<td>0.66</td>
</tr>
</tbody>
</table>

**NO Differences**

*References:*

- *N Engl J Med* 372;21
- NEJM.org
- May 21, 2015
Short Course Antibiotics for Intra-abdominal Infection

we calculated that a sample of 505 patients per group would be required to give the study 90% power to detect a 10% difference in complication rates, assuming a 30% complication rate among controls and assuming a dropout rate of 10%, at an alpha level of 0.05. After the first interim

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (N=250)</th>
<th>Experimental Group (N=257)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Surgical-site i</td>
<td></td>
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<td>0.43</td>
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<td>Recurrent int</td>
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<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>Time to event</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>19.0±1.0</td>
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<td>0.66</td>
</tr>
</tbody>
</table>

NO Differences

N ENGL J MED 372;21 NEJM.ORG MAY 21, 2015
Biomarker-based studies also support shorter treatment

Use of procalcitonin to reduce patients’ exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial


30% vs 26% at 60 days
Biomarker-based studies also support shorter treatment

BUT, only 50% clinician adherence to procalcitonin algorithm

Bouadma *Lancet* 2010
How long should we treat patients with bloodstream infection?
The Clinical Problem

ICU bloodstream infections are common
15% point prevalence

ICU bloodstream infections are serious
2-3fold mortality

Delayed treatment associated with higher mortality
8% increase per hour delay

Vincent JAMA 2009; Valles CID 1997; Kumar CCM 2006
 BALANCE Trial

Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness
Research Question

Is shorter duration antibiotic therapy (~7 days) as effective as longer duration antibiotic therapy (~14 days) for critically ill patients with bacteremia?
Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis

Thomas C Havey, Robert A Fowler, and Nick Daneman

Single-Centre Retrospective Study

Multi-Centre Retrospective Study

Multi-centre randomized controlled trial
Short VS Long Antibiotic Treatment for Bacteremia

National survey of Canadian infectious diseases specialists

National survey of Canadian critical care specialists
Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis

Thomas C Havey¹, Robert A Fowler¹,² and Nick Daneman¹,³*
There is no benefit from excessive antibiotic durations.
Bacteremic Patients

Clinical Cure

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Short Duration</th>
<th>Long Duration</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chowdary</td>
<td>28 Events 33 Total</td>
<td>32 Events 33 Total</td>
<td>0.88 [0.75, 1.02]</td>
</tr>
<tr>
<td>Jeremiah</td>
<td>5 Events 5 Total</td>
<td>4 Events 4 Total</td>
<td>1.00 [0.68, 1.46]</td>
</tr>
<tr>
<td>Siegel</td>
<td>0 Events 2 Total</td>
<td>3 Events 4 Total</td>
<td>0.24 [0.02, 3.19]</td>
</tr>
<tr>
<td>Tellier</td>
<td>12 Events 12 Total</td>
<td>8 Events 8 Total</td>
<td>1.00 [0.83, 1.21]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>52 Events 49 Total</td>
<td>100.0%</td>
<td>0.88 [0.77, 1.01]</td>
</tr>
</tbody>
</table>

Total events 45 47
Heterogeneity: $\chi^2 = 3.15, df = 3 (P = 0.37); I^2 = 5$
Test for overall effect: $Z = 1.86 (P = 0.06)$

Figure 2 Forest plot for outcome of clinical cure among bacteremic subgroups of randomized trials of shorter versus longer antibiotic treatment. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

Survival

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Short Duration</th>
<th>Long Duration</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaudhr</td>
<td>5 Events 6 Total</td>
<td>7 Events 8 Total</td>
<td>0.95 [0.61, 1.48]</td>
</tr>
<tr>
<td>Runyon</td>
<td>9 Events 9 Total</td>
<td>15 Events 17 Total</td>
<td>1.10 [0.87, 1.39]</td>
</tr>
<tr>
<td>Siegel</td>
<td>1 Events 2 Total</td>
<td>4 Events 4 Total</td>
<td>0.56 [0.17, 1.79]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17 Events 29 Total</td>
<td>100.0%</td>
<td>0.97 [0.76, 1.23]</td>
</tr>
</tbody>
</table>

Total events 15 26
Heterogeneity: $\chi^2 = 2.07, df = 2 (P = 0.36); I^2 = 3$
Test for overall effect: $Z = 0.26 (P = 0.79)$

Figure 4 Forest plot for outcome of survival among bacteremic subgroups of randomized trials of shorter versus longer antibiotic treatment. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.
Systematic review of treatment duration in bacteremia

Systematic review of treatment duration in syndromes complicated by bacteremia

Single centre Retrospective Study

Multi-Centre Retrospective Study

Multi-centre randomized controlled trial
Short VS Long Antibiotic Treatment for Bacteremia
Case 1

A 65 year old woman develops fever and hypotension 2 weeks after admission to the critical care unit. She receives early resuscitation including vasopressor support. Blood and urine cultures are sent and she is started on an empiric antimicrobial agent.

Over the next 48 hours, vasopressor requirements are gradually weaned down and the patient is off vasopressors by the time microbiology results are available at 48h. Blood culture grew E.coli susceptible to the empiric agent she was receiving. Urine culture was negative. Abdominal ultrasound is negative. Her previously inserted femoral venous catheter is removed as a probable source of her bacteremia.
Are typical durations appropriate?

- 53% “too long”
- 24% “appropriate”
- 10% “too short”
- 13% “I don’t know”
Are typical durations appropriate?

- 53% "too long"
- 24% "appropriate"
- 10% "too short"
- 13% "I don't know"

Percent of Respondents that Would Enroll Patients in Trial of 7 vs 14 day Antibiotic Treatment

- Central vascular catheter bloodstream infection
- Bacteremic pneumonia
- Bacteremic urinary tract infection
- Bacteremic intra-abdominal infection
- Bacteremic soft tissue infection

Bacteremic Syndrome

Legend:
- Infectious Diseases Specialists
- Critical Care Specialists
Systematic review of treatment duration in bacteremia

Systematic review of treatment duration in syndromes complicated by bacteremia

National survey of Canadian infectious diseases specialists

National survey of Canadian critical care specialists

Single-Centre Retrospective Study

Multi-Centre Retrospective Study

Multi-centre randomized controlled trial
Short VS Long Antibiotic Treatment for Bacteremia
Canadian Multicentre, Retrospective, Observational Cohort Study

- 14 ICUs across 6 Canadian provinces
- n=1202 patients
- Most recent, consecutive bacteremic patients in critical care
<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>Treatment duration (Median, days)</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>335</td>
<td>14</td>
<td>9-18</td>
</tr>
<tr>
<td>Venous/arterial catheter</td>
<td>178</td>
<td>13</td>
<td>8-15</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>198</td>
<td>15</td>
<td>11-18</td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>143</td>
<td>13</td>
<td>9-18</td>
</tr>
<tr>
<td>Skin &amp; soft tissue</td>
<td>82</td>
<td>15</td>
<td>10-23</td>
</tr>
<tr>
<td>Hepato-biliary</td>
<td>67</td>
<td>13</td>
<td>10-18</td>
</tr>
<tr>
<td>Others</td>
<td>50</td>
<td>15</td>
<td>11-20</td>
</tr>
<tr>
<td>Unknown source</td>
<td>121</td>
<td>11</td>
<td>6-15</td>
</tr>
<tr>
<td>Overall</td>
<td>1176*</td>
<td>14</td>
<td>9-17</td>
</tr>
</tbody>
</table>
Antibiotic Treatment Duration

![Histogram showing the distribution of days of adequate antimicrobial treatment for shorter and longer duration.](image)
What about outcomes according to treatment duration?

Observational studies assessing impact of duration of treatment on patient outcomes are limited by:

- **survivor bias** (patients must survive long enough to be classified as receiving longer treatment) > *shorter treatments look worse*

- **indication bias** (clinicians select sicker patients to receive longer duration treatment) > *longer treatment looks worse*
Depending upon the time point you choose to include patients in the observational study, longer treatment can be associated with either:

- a 31% increase in survival or
- an 18x worse survival

These questions cannot be adequately answered by observational studies.
Systematic review of treatment duration in bacteremia

Systematic review of treatment duration in syndromes complicated by bacteremia

National survey of Canadian infectious diseases specialists

National survey of Canadian critical care specialists

Single-Centre Retrospective Study

Multi-Centre Retrospective Study

Multi-centre RCT 7 vs 14 days Antibiotic Treatment for Bacteremia
BALANCE RCT: General Design

Central randomization

Antibiotic regimen as per clinical team

Intervention = the date of stoppage: 7 vs 14d

Open label, no placebo

not practical to use placebos (>100 different pathogens; >60 different antibiotic regimens in retrospective study)

Prolonged allocation concealment to day 7
Inclusion Criteria

1. patient is in the ICU at time the blood culture is reported as positive

AND

2. patient has a positive blood culture with pathogenic bacteria
Exclusion Criteria

1. patient already enrolled in the trial
2. patient has severe immunocompromise
   i. PMN<0.5x10^9/L
   ii. immunosuppression for solid organ or bone marrow transplant
3. prosthetic heart valve or synthetic endo-vascular graft
4. syndrome with well-defined requirement for prolonged treatment
   i. infective endocarditis
   ii. osteomyelitis/septic arthritis
   iii. undrainable/undrained abscess
   iv. unremovable/unremoved prosthetic-associated infection
5. single positive blood culture for potential contaminant
   i. coagulase negative staphylococcus
   ii. *Bacillus* spp.
   iii. *Corynebacterium* spp.
   iv. *Aerococcus* spp.
6. patient has a positive blood culture with *Staphylococcus aureus*
7. patient has a positive blood culture with *Candida* or fungus
Primary outcome

• 90 day survival
### Secondary outcomes

**Hypothesis:**
Shorter duration treatment

**NON-INFERIOR**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>hospital mortality</td>
</tr>
<tr>
<td>b</td>
<td>ICU mortality</td>
</tr>
<tr>
<td>c</td>
<td>relapse of bacteremia</td>
</tr>
<tr>
<td>d</td>
<td>ICU length of stay</td>
</tr>
<tr>
<td>e</td>
<td>hospital length of stay</td>
</tr>
<tr>
<td>f</td>
<td>mechanical ventilation duration</td>
</tr>
<tr>
<td>g</td>
<td>vasopressor duration</td>
</tr>
<tr>
<td>h</td>
<td>decline in procalcitonin levels</td>
</tr>
</tbody>
</table>

**Hypothesis:**
Shorter duration treatment

**SUPERIOR**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>antibiotic-free days</td>
</tr>
<tr>
<td>j</td>
<td>antibiotic allergy and adverse events</td>
</tr>
<tr>
<td>k</td>
<td><em>C. difficile</em> infection</td>
</tr>
<tr>
<td>l</td>
<td>infection/colonization with antibiotic resistant organisms</td>
</tr>
<tr>
<td>m</td>
<td>rectal microbiome diversity</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>non-inferiority margin</td>
<td>4%</td>
</tr>
<tr>
<td>baseline mortality</td>
<td>22%</td>
</tr>
<tr>
<td>alpha</td>
<td>0.025</td>
</tr>
<tr>
<td>power</td>
<td>80%</td>
</tr>
<tr>
<td>sample size</td>
<td>3598</td>
</tr>
</tbody>
</table>
Substudies

Procalcitonin over time

Microbiome diversity
Pilot RCT:
Primary research question

Is it feasible to perform a large RCT among critically ill patients with bloodstream infection to determine whether shorter duration antibiotic treatment (7d) is non-inferior to longer duration treatment (14d)?
Pilot RCT: Primary Outcomes

• Recruitment rate goal = 1 patient / site / month

• Protocol adherence
  • 90% of treatment courses 7 ± 2 days in shorter duration arm
  • 90% of treatment courses 14 ± 2 days in longer duration arm
Assessed for eligibility (n= 1159)

Meet Exclusion Criteria= 801
- 5 patients already enrolled in the trial
- 72 patients had severe immune system compromise
- 29 patients had a prosthetic valve or synthetic endovascular graft
- 125 patients had documented or strong suspicion of syndrome with well-defined requirement for prolonged treatment
- 394 patients had a single positive blood culture with a common contaminant organism
- 150 patients had Staphylococcus aureus
- 26 patients had Candida spp. or other fungal species

Eligible (n= 358)

Randomized (n= 115)
- 48 patient or substitute decision maker (SDM) declined consent
- 35 patient unable to give consent and SDM not available
- 71 ICU physician declined consent, reason
- 89 consent not obtained due to other reason

Non Randomized (n= 243)
Recruitment

Target (1/month/site) vs. Enrolled
Results .... CCCF 2017
Acknowledgments

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– Rob Fowler

co-investigators
– Sean Bagshaw
– Deborah Cook
– Peter Dodek
– Rick Hall
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– Francois Lamontagne
– Francois Lauzier
– John Marshall
– Claudio Martin
– Lauralyn McIntyre
– John Muscedere
– Steve Reynolds
– Andrew Seely
– Tom Stelfox
– Pierre Aslanian
– Liz Wilcox
– Mike Detsky
– Emmanuel Charbonney

ID co-investigators
– Alex Carignan
– Julie Bestman-Smith
– Linda Taggart
– John Conly
– Wendy Sligl
– Anand Kumar
– Steve Reynolds
– Victor Leung
– Valérie Martel-Laferrière
– Andre Poirier

Central study coordinator
– Asgar Rishu

Site coordinators
– N. Baig / S. Taylor
– V. Alcuaz
– L. Julien
– N. Marten/O. Gutierrez
– N. Poitras/M.H. Masse / É. Carbonneau/H. Fournier
– M. C. Tremblay/D. Barriault
– O. Smith/G. Sandhu/K. Salway
– E. Campbell/S. Imerovski
– I. Watpool/R. Porteous / B. Gomes/S. Acres
– S. Willems
– M. Hunt/I. Georgescu
– S. Ruddell/J. Booth
– M. Lebrasseur/F. Benettaib
– D. Tapps
– S. Shah/E. Tamber
– B. Kosky/L. Stenyk

International leads

Switzerland:
– Philippe Eggimann
– Jean-Luc Pagani
– Jean-Pierre Revelly
– Yok Ai Que

New Zealand:
– Shay McGuinness
– Colin McArthur
– Sally Roberts
– Rachael Parke

Australia:
– Steve Webb
– Yahya Shehabi
– David Paterson

UK:
– Tim Walsh
– John Simpson
– Paul Dark
– Thomas Hellyer

Saudi Arabia:
– Yaseen Arabi
– Basem Alraddadi

Germany:
– Frank Bloos

Us:
– Perren Cobb

Pediatric co-PIs
– Sandra Pong
– Jamie Hutchinson
– Melissa Parker
– Michelle Science
– Jeff Pernica
– Patricia Fontela
– Ron Gottesman
– Philippe Jouvet
– Elaine Gilfoyle
– Gonzalo Garcia

Others
– Ruxandra Pinto
– Wei Xiong
– Tom Havey
– Kevin Shore

CLARITY/Idatafax
– Nicole Zytaruk
– Lisa Buckingham

CCCTG
Canadian Critical Care Trials Group
Ten most prescribed antimicrobial by DDDs per 1,000 patient days reported by CNISP participating hospitals between 2009 and 2013 in Canada.