TREATMENT OF BACTEREMIA - THE CANADIAN EXPERIENCE -

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Disclosure

There are only two things we don’t know in Infectious Diseases…

Which antibiotic to use and how long to use it for
Overview

1) How long to use it for …

- Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) research program

2) Which antibiotic to use …

- the WISCA - a novel approach to selecting empiric treatment for critical care
- impact of inadequate vs. adequate initial empiric treatment on mortality in Canadian critically ill patients with bacteremia/candidemia
Research Question

- Is shorter duration antibiotic treatment (~7 days) non-inferior to longer duration antibiotic treatment (~14 days) for preventing mortality among critically ill patients with bloodstream infection?
BALANCE – research trajectory

- Systematic review of treatment duration in bacteremia
- Systematic review of treatment duration in syndromes complicated by bacteremia
- National survey of Canadian infectious diseases and critical care specialists
- Single centre retrospective study

Multicentre retrospective Study

Pilot RCT

BALANCE Main RCT
BALANCE – research trajectory

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Multicentre retrospective Study

Pilot RCT

BALANCE Main RCT
Survey: Methods

- Canadian national practice survey
  - Infectious diseases specialists
  - Critical care specialists

- piloting and sensibility testing

- Surveymonkey™

- 2 electronic mail-outs to national societies (AMMI, CCCS)

- additional detailing at CCCTG
An 84 year old man was found confused in his home and admitted to the ICU with urosepsis. The patient initially required vasopressor support, but this has been weaned off by the time the microbiology result is available at 48h. Urine and blood cultures grew Klebsiella pneumoniae susceptible to the empiric agent he has been receiving.

How long an antibiotic course would you typically recommend for this patient?

0,1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,>28 days
Survey: Respondents

- n=172
  - 103 ID specialists
  - 67 ICU specialists
  - 2 ID/ICU combined specialists

- majority from academic hospitals (81%)

- wide spectrum of clinical experience
  - ¼ with ≥ 20 years in practice
Host Factors

- most would not alter treatment based on baseline host characteristics

- advanced age: 92% no change
- CHF: 95% no change
- COPD: 88% no change
- cirrhosis: 76% no change
- CKD: 76% no change
- malignancy: 66% no change
Clinical Response

- most would not alter treatment based on day 3 reassessments indicating:

  - persistent fever 69% no change
  - persistent vasopressor 78% no change
  - persistent ventilator 90% no change
Systematic review of treatment duration in bacteremia
Systematic review of treatment duration in syndromes complicated by bacteremia
National survey of Canadian infectious diseases and critical care specialists
Single centre retrospective study

AHSC-AFP Innovation Fund Grant
Physicians Services Incorporated Health Research Grant

Multicentre retrospective study
Pilot RCT
BALANCE Main RCT

Canadian Critical Care Trials Group

Duration of Antimicrobial Treatment for Bacteremia in Canadian Critically Ill Patients
Nick Duneman, MD; Asgar H. Rish, MBBS; Wei Xiong, MSc; Sean M. Bagshaw, MD; Peter Dodek, MD; Richard Hall, MD; Anand Kumar, MD; Francois Lamontagne, MD; Francois Lussier, MD; John Marshall, MD; Claudius M. Martin, MD; Laurenza McIntyre, MD; John Muscedere, MD; Steve Reynolds, MD; Henry T. Stelfox, MD; Deborah J. Cook, MD; Robert A. Fowler, MD; on behalf of the Canadian Critical Care Trials Group

CCM in Press
Multicentre Retrospective Study: Primary Objective

- To describe *actual* antibiotic treatment durations for patients with bloodstream infections across a nationally representative sample of Canadian ICUs
- *Hypothesis: there will be extensive heterogeneity and collective equipoise for a trial*
Secondary Objectives

1. To identify host, syndrome and pathogen characteristics associated with selection of shorter versus longer antibiotic durations

2. To explore association of treatment duration and mortality
Methods:
Overview

• multicentre
• retrospective
• observational (cohort) study
• 14 sites
• 100 most recent, consecutive bacteremic patients in critical care
Participating Sites across Canada

- **Ontario**
  - Toronto
    - Sunnybrook
    - St. Michael’s
  - Kingston
    - Kingston General Hospital
  - London
    - London Health Sciences Centre
  - Ottawa
    - Ottawa Hospital
- **Nova Scotia**
  - Halifax
    - Queen Elizabeth II
- **Quebec**
  - Quebec City
    - Hopital de l’Enfant-Jesus
  - Sherbrooke
    - Centre Hospitalier Universitaire de Sherbrooke
- **Manitoba**
  - Winnipeg
    - St. Boniface
- **Alberta**
  - Calgary
    - Foothills Medical Centre
- **British Columbia**
  - Vancouver
    - Royal Columbian
    - St. Paul’s
ELIGIBILITY CRITERIA FORM 1.1

Eligibility Criteria: Must meet both inclusion criteria, and none of exclusion criteria

Inclusion Criteria

1. Patient has a positive blood culture with a pathogenic organism (gram stain or culture growth of pathogenic bacterial organisms, see exclusion criteria)?
   
2. Patient is critically ill at the time blood culture collected as defined by the following: was admitted to an intensive care unit (ICU) / area of the hospital where critically ill patients receive treatment (level II ICU, level III ICU, or bed-spaced but under care of ICU physicians)?

Exclusion Criteria

3. Patient previously enrolled in this study?

4. Positive blood culture representing probable contamination, meaning a single specimen with one of these organisms?
   - coagulase negative Staphylococci
   - Bacillus spp. (“aerobic spore forming bacillus”)
   - Corynebacterium spp. (“diptheroids”)
   - Propionobacterium spp.
   - Aerococcus spp.
   - Micrococcus spp.

5. Focus of infection (physician diagnosis) for which the need for very prolonged treatment is well established?
   - infective endocarditis
   - osteomyelitis
   - septic arthritis
   - undrainless abscess
   - unremovable prosthetic material
## Actual Durations of Treatment for Bacteremia in Canadian Critically Ill patients

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Median, d</th>
<th>Q1</th>
<th>Q3</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1,176</td>
<td>14.0</td>
<td>9.0</td>
<td>17.5</td>
<td>1.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>335</td>
<td>14.0</td>
<td>9.0</td>
<td>18.0</td>
<td>1.0</td>
<td>75.0</td>
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<tr>
<td>Urinary tract</td>
<td>198</td>
<td>15.0</td>
<td>11.0</td>
<td>18.0</td>
<td>1.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Vascular catheter</td>
<td>178</td>
<td>13.0</td>
<td>8.0</td>
<td>15.0</td>
<td>1.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>143</td>
<td>14.0</td>
<td>9.0</td>
<td>18.0</td>
<td>1.0</td>
<td>56.0</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>82</td>
<td>15.0</td>
<td>10.0</td>
<td>21.0</td>
<td>1.0</td>
<td>64.0</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>67</td>
<td>14.0</td>
<td>10.0</td>
<td>18.0</td>
<td>1.0</td>
<td>59.0</td>
</tr>
<tr>
<td>Others</td>
<td>50</td>
<td>15.0</td>
<td>11.0</td>
<td>19.0</td>
<td>2.0</td>
<td>43.0</td>
</tr>
<tr>
<td>Unknown source</td>
<td>123</td>
<td>11.0</td>
<td>6.0</td>
<td>15.0</td>
<td>1.0</td>
<td>56.0</td>
</tr>
</tbody>
</table>

Q1 = first quartile, Q3 = third quartile.

*The total of 1,176 exceeds the number of patients with evaluable treatment durations (916) because some cases of bacteremia were attributed to more than one potential source.*
Actual Durations of Treatment for Bacteremia in Canadian Critically Ill patients
Predictors of Receiving Shorter versus Longer Treatment Duration

• Among patient factors
  • COPD associated with shorter treatment

• Among pathogen factors
  • Coagulase-negative staphylococci associated with shorter treatment

• Among sources of bacteremia
  • Urinary tract source associated with longer treatment
  • Unknown source associated with shorter treatment
Survivor Bias Precludes a Valid Assessment of the Association Between Treatment Duration and Survival
BALANCE – research trajectory

Systematic review of treatment duration in bacteremia
Systematic review of treatment duration in syndromes complicated by bacteremia
National survey of Canadian infectious diseases and critical care specialists
Single centre retrospective study

Multicentre retrospective Study

BALANCE Pilot RCT
n=115
MOHLTC AFP Innovation Fund
Primary outcomes:
- recruitment rate
- protocol adherence

BALANCE Main RCT
n=3598
CIHR bridge funding
Primary outcome:
90d mortality (non-inferiority)
Overview

1) How long to use it for …

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2) Which antibiotic to use …

- the WISCA - a novel approach to selecting empiric treatment for critical care

- impact of inadequate vs. adequate initial empiric treatment on mortality in Canadian critically ill patients with bacteremia/candidemia
Weighted Incidence Syndromic Combination Antibiogram (WISCA)

Traditional Antibiogram

WISCA

- likelihood for coverage of a ‘syndrome’ instead of bug
- take into account potential for polymicrobial infections
- take into account use of multi-drug regimens

Antimicrobial Susceptibilities of Bacterial Isolates from ICUs (CRCU, CVICU, D4ICU, B5ICU, RTBC) (% susceptible)

<table>
<thead>
<tr>
<th>Gram Positive Organisms</th>
<th>PEN</th>
<th>CLOX</th>
<th>CEF</th>
<th>CLIN</th>
<th>ERY</th>
<th>VAN</th>
<th># of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>0*</td>
<td>87</td>
<td>87</td>
<td>80</td>
<td>74</td>
<td>100</td>
<td>169</td>
</tr>
<tr>
<td>Coag neg staph</td>
<td>0*</td>
<td>41</td>
<td>41</td>
<td>43</td>
<td>26</td>
<td>100</td>
<td>60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram Negative Organisms</th>
<th>AMP</th>
<th>CEF</th>
<th>CFX</th>
<th>GENT</th>
<th>TOBRA</th>
<th>TMP - SMX</th>
<th>CIP</th>
<th>CEFTAZ</th>
<th>PIP - TAZO</th>
<th>MERO</th>
<th># of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>44</td>
<td>74</td>
<td>83</td>
<td>90</td>
<td>91</td>
<td>71</td>
<td>74</td>
<td>84</td>
<td>73</td>
<td>100</td>
<td>128</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>0</td>
<td>83</td>
<td>87</td>
<td>97</td>
<td>94</td>
<td>89</td>
<td>91</td>
<td>87</td>
<td>83</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>0</td>
<td>0</td>
<td>70</td>
<td>97</td>
<td>94</td>
<td>94</td>
<td>97</td>
<td>69</td>
<td>65</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Other coliforms</td>
<td>18</td>
<td>18</td>
<td>96</td>
<td>93</td>
<td>89</td>
<td>87</td>
<td>88</td>
<td>96</td>
<td>95</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>0</td>
<td>0</td>
<td>93</td>
<td>98</td>
<td>0</td>
<td>77</td>
<td>75</td>
<td>66</td>
<td>74</td>
<td>92</td>
<td>92</td>
</tr>
</tbody>
</table>
Applying WISCA to Critical Care Infections

- retrospective cohort study
- Sunnybrook Health Sciences Centre
- critical care infections reported to Critical Care Information System 2010-2013
  - ventilator associated pneumonia (VAP)
    - n=107
  - catheter-related bloodstream infection (CRBSI)
    - n=56
- generated WISCA for
  - VAP
  - CRBSI
  - VAP or CRBSI
- included all culture positive cases (including polymicrobial cases)
- examined likelihood of coverage for monotherapy and dual-therapy regimens
- compared likelihood of adequate coverage for WISCA regimens to actual adequate coverage received by 12, 24 and 48h from culture collection

Randhawa *Crit Care* 2014
Actual time to adequate coverage

Figure 1 Time to first adequate antimicrobial treatment for critical care infection. The gray bars represent the cumulative percentage of patients with ventilator-associated pneumonia or catheter-related bloodstream infection receiving adequate empiric antimicrobial treatment as a function of time from index microbiology specimen collection.
BUT, will earlier adequate antibiotic treatment lead to improved outcomes for patients with bloodstream infection?

<table>
<thead>
<tr>
<th>WISCA empiric regimens</th>
<th>Percentage of VAP or CRBSI with documented adequate coverage by this regimen (n = 163)</th>
<th>Excess percentage of adequate coverage compared to retrospective cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>110 (67%)</td>
<td>+30% +16% −8%</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>75 (46%)</td>
<td>+9% −5% −29%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>77 (47%)</td>
<td>+10% −4% −28%</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>77 (47%)</td>
<td>+10% −4% −28%</td>
</tr>
<tr>
<td>Pip-Tazo.</td>
<td>103 (63%)</td>
<td>+26% +12% −12%</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>93 (57%)</td>
<td>+20% +6% −18%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>121 (74%)</td>
<td>+37% +23% −3%</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>30 (18%)</td>
<td>−19% −33% −57%</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>67 (41%)</td>
<td>+5% −10% −34%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>68 (42%)</td>
<td>+6% −9% −33%</td>
</tr>
<tr>
<td><strong>Dual combination therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem + Vancomycin</td>
<td>152 (93%)</td>
<td>+56% +42% +18%</td>
</tr>
<tr>
<td>Ertapenem + Vancomycin</td>
<td>127 (78%)</td>
<td>+41% +27% +3%</td>
</tr>
<tr>
<td>Pip-Tazo. + Vancomycin</td>
<td>144 (88%)</td>
<td>+51% +37% +13%</td>
</tr>
<tr>
<td>Ceftazidime + Vancomycin</td>
<td>141 (87%)</td>
<td>+50% +36% +12%</td>
</tr>
<tr>
<td>Ceftriaxone + Vancomycin</td>
<td>117 (72%)</td>
<td>+35% +21% −3%</td>
</tr>
<tr>
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<td>151 (93%)</td>
<td>+56% +42% +18%</td>
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</tr>
<tr>
<td>Tobramycin + Cloxacillin</td>
<td>116 (71%)</td>
<td>+34% +20% −4%</td>
</tr>
<tr>
<td>Meropenem + Tobramycin</td>
<td>126 (77%)</td>
<td>+40% +26% +2%</td>
</tr>
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</tr>
<tr>
<td>Ceftazidime + Tobramycin</td>
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<td>+26% +12% −12%</td>
</tr>
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<td>+34% +20% −4%</td>
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</tr>
</tbody>
</table>
The Effect of Inadequate Initial Empiric Antimicrobial Treatment on Mortality in Critically Ill Patients with Bloodstream Infection

• sub-study of BALANCE multi-centre observational study

• examined association of inadequate initial empiric treatment and mortality

• inadequate initial empiric treatment
  • not receiving at least one dose of an antimicrobial to which the pathogen(s) were all susceptible within one day of blood culture collection

• multivariable logistic regression model
  • accounting for patient and pathogen characteristics
  • random effect to account for ICU site
Inadequate Initial Empiric Antimicrobial Treatment and Mortality

- found a statistically significant interaction (effect-modification) between bacteremia/candidemia AND association of adequate treatment and mortality

- therefore, had to look separately at association of adequate treatment and mortality for
  - bacteremia (n=1,190)
  - candidemia (n=93)
# Inadequate Initial Empiric Antimicrobial Treatment and Mortality

<table>
<thead>
<tr>
<th>Type of Bloodstream Infection</th>
<th>Adjusted Odds Ratio for Mortality with Inadequate Initial Treatment</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>OR 1.02</td>
<td>0.83-1.61</td>
<td>0.38</td>
</tr>
<tr>
<td>Candidemia</td>
<td>OR 2.89</td>
<td>1.05-7.99</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Savage *Clin Inf Dis* In Submission
Robust result in Sensitivity Analyses

1. excluding patients with early deaths
2. defining adequate treatment with 2d instead of 1d window
3. excluding patients that received no antimicrobial treatment

Savage *Clin Inf Dis* In Submission
Time to finalization of blood culture results

- Bacteremic (1,096)
- Candidemic (93)
Time to adequate treatment

- **Bacteremia (1,032)**
- **Candidemia (75)**
Summary

How Long to Treat Bacteremia

- there is a lack of high grade evidence for treatment duration in bacteremia
- self-reported treatment recommendations are highly variable, and usually prolonged
- actual treatment durations are highly variable, and usually prolonged
- there is equipoise for a trial of 7 vs 14d treatment
- stay tuned for:

Which Drug to Use for Bacteremia

- consider using WISCAs to guide syndromic empiric treatment for infections in critically ill patients
- can then use traditional hospital antibiograms once a pathogen is identified
- it’s unclear which bacteremic patients are most in need of initial adequate empiric coverage
- candidemic patients may be particularly prone to poor outcomes with inadequate treatment
- we need better prediction rules and/or early diagnostic tests for candidemia
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  – John Muscedere
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  – Elaine Gilfoyle
  – Gonzalo Garcia

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

  • New Zealand:
    – Shay McGuinness
    – Colin McArthur
    – Sally Roberts

  • Australia:
    – Steve Webb
    – Yahya Shehabi
    – David Paterson

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

  • Saudi Arabia:
    – Yaseen Arabi

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