Interventions That Work in Hospitals

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Agenda for Today

• Systematic Review of Interventions to Promote Prudent Antibiotic Prescribing
  – Education or Enforcement?
  – Clinical & microbiological outcomes
  – How far have we come with antibiotic stewardship?

• Implications for research

• Implications for practice
Cochrane Effective Practice and Organisation of Care Group

• Acceptable study designs
  – Interrupted time series
  – Controlled before and after studies
  – Patient randomised controlled trials
  – Cluster randomised controlled trials

www.epoc.uottawa.ca
Cochrane Hospital Antibiotic Review

• Joint Working Party of the British Society for Antimicrobial Chemotherapy and the Hospital Infection Society

• The primary aim was to systematically review the literature to identify interventions that alone, or in combination, are effective in promoting prudent antibiotic prescribing to hospital inpatients.
Prudent Antibiotic Prescribing

• Use of antimicrobials in the most appropriate way for the treatment, or prevention, of human infectious diseases.

• Key elements in decision making:
  – Diagnosis (or presumed diagnosis)
  – Evidence of clinical effectiveness
  – Likely benefits
  – Safety
  – Cost (in comparison with relevant alternative choices)
  – Propensity for the emergence of resistance

• Key decisions:
  – Is an antibiotic needed?
  – If needed, choice of drug, route, dosage, frequency and duration of administration have been rigorously determined.
743 Papers Since 1980
393 Not eligible
350 Eligible

First Cut
N=107 (31%)

Invalid design
N=243 (69%)

Included
N=66 (20%)
+2 secondary

Excluded
N=39 (11%)

Inadequate Time Series
N=79 (22%)

Uncontrolled Before & After
N=164 (47%)

www.update-software.com/cochrane/
Evaluation Types

- 43 Interrupted Time Series
- 13 Randomised Controlled Trials
- 2 Controlled Clinical Trials
- 1 cluster RCT
- 1 cluster CCT
- 6 Controlled Before & After
Interrupted time series (ITS)
- minimum criteria

• Clearly defined point in time when the intervention occurred.
• At least 3 data points before and after the intervention
• Both criteria must be met for a study to be included in a Cochrane review
Conclusions: Methods

- Only 20% of published literature meets minimum standards
- 3 points is an absolute but very bare minimum for ITS
- Resist the temptation to reduce time series into averages
Results 1: 66 Studies from Eleven Countries

- USA (42)
- UK (8)
- Canada (4)
- Australia (2)
- France (2)
- The Netherlands (2)
- Thailand (2)
- Brazil (1)
- Colombia (1)
- Norway (1)
- Spain (1)
Number of hospitals in which interventions were implemented

- 57 in single hospitals
- 4 in 2-3 hospitals
- 5 in $\geq 10$ hospitals (range 10-36)
Objectives of interventions
1. Decrease antibiotic prescribing (n=57)
2. Increase antibiotic prescribing (n=6)
3. Decrease and increase antibiotic prescribing—rapid tests (n=3)

Targets of interventions
1. Choice, dosage, route of administration (n=61)
2. Duration (n=3)
3. Timing (n=3)
4. Decision to give an antibiotic (n=1)
Outcome Measures

1. Antibiotic prescribing, n=51
   – drug, dose, route, interval, duration

2. Clinical, n=14
   – LOS, response rate, mortality rate

3. Microbiological, n=16
   – *C. difficile*, colonisation/infection with antibiotic-resistant bacteria
Deliverer and Outcomes

- Pharmacist (n=22)
- ID/microbiology (n=17)
- Antimicrobial Team (n=11)
- Antibiotic Policy (n=7)
- Feedback (n=5)
- Departmental physician (n=4)

Drug
Microbial
Clinical
Increase Antibiotic Use: Drug Outcomes

- 2nd intra-operative dose
- Cesareans given prophylaxis
- Gentamicin peak >4mg/l
- % antibiotics increased
- Bacteraemia started on antibiotics
- % severe pneumonia on IV antibiotics
- CAP antibiotics within 4h
Increase Antibiotic Use: Clinical Outcomes

- **Prophylaxis**: wound infections
- **CAP**: mortality
- **CAP**: mortality
- **Bacteraemia**: mortality
- **Bacteremia**: infections not responding

![Graph showing clinical outcomes associated with increased antibiotic use.](chart.png)
Decrease Antibiotic Prescribing: Drug Outcomes

<table>
<thead>
<tr>
<th>Design</th>
<th>N</th>
<th>Significant effect</th>
<th>Trend (p&lt;0.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBA, CCT, RCT</td>
<td>14</td>
<td>10 (71%)</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>ITS</td>
<td>33</td>
<td>26 (79%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>All</td>
<td>47</td>
<td>36 (77%)</td>
<td>5 (11%)</td>
</tr>
</tbody>
</table>
Clinical Outcomes of Reduced Prescribing: Mortality

Relative Risk of Mortality (Intervention/Control)

- IV oral switch
- ICU policy
- ICU shorten
- AMT
- AMT
Clinical Outcomes of Reduced Prescribing: Readmission

Relative Risk of Readmission (Intervention/Control)

- IV oral switch
- AMT
- AMT
<table>
<thead>
<tr>
<th>Educational</th>
<th>Enforcement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend change: 16</td>
<td>Expert approval: 14</td>
</tr>
<tr>
<td>General education: 13</td>
<td>Removal/restriction: 9</td>
</tr>
<tr>
<td>Reminders: 8</td>
<td>Compulsory order forms: 5</td>
</tr>
<tr>
<td>Guidelines: 5</td>
<td>Cycling/rotation: 4</td>
</tr>
<tr>
<td>Audit and feedback: 4</td>
<td>Therapeutic substitution: 3</td>
</tr>
<tr>
<td>Care pathway: 3</td>
<td>Automatic stop-order: 2</td>
</tr>
<tr>
<td>Opinion leaders: 2</td>
<td>Compulsory computer: 1</td>
</tr>
</tbody>
</table>
# ITS duration in months

<table>
<thead>
<tr>
<th></th>
<th>Pre intervention</th>
<th>Post intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Education</td>
<td>20</td>
<td>3-36</td>
</tr>
<tr>
<td>Enforcement</td>
<td>18</td>
<td>1-48</td>
</tr>
<tr>
<td>Mixed</td>
<td>17</td>
<td>6-36</td>
</tr>
</tbody>
</table>
Meta regression 1

• Drug outcomes, monthly intervals
• 7 Educational vs 7 Enforcement
• Restrictive interventions 3.6-fold additional immediate effect (CI from 2.9- to 4.2-fold)
• Unable to compare sustained effects
Effect of Restriction Can Wear Off

![Graph showing vancomycin doses per 1000 patient days over months, with immediate and sustained effects highlighted.]

<table>
<thead>
<tr>
<th>Δ (post-intervention – pre-intervention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
</tr>
<tr>
<td>Sustained</td>
</tr>
</tbody>
</table>

|  
|-----------------|
| **P**          |
| Immediate      | 0.05 |
| Sustained      | <0.001 |
If practice was already changing in the intended direction pre-intervention the immediate effect was only 25% compared with studies where practice was not changing or getting worse.
Conclusions: Drug & Clinical

- Interventions to increase prescribing more likely to include clinical outcome
- Multidisciplinary teams choose multidisciplinary outcomes
- More interventions needed on duration of antibiotic treatment & decision to prescribe
- Enforcement interventions have a bigger short term impact versus Educational interventions
  
BUT WHAT ABOUT LONG TERM?

- Standardised interval (months) and post-intervention (1 year?) would help comparison
- If it ain’t broke don’t fix it
16 Studies with Microbiological Data

- Micro Only, 10
- Drug & Clin & Micro, 1
- Drug & Micro, 4
- Micro & Clinical, 1
Epidemic of ESBL *Enterobacter cloacae*

Policy Change

Cases

1989 1990
de Champs et al, J Hosp Infect, 1994, 28: 219-229
Common Threats to Validity = Plausible Alternative Explanations

- Unplanned intervention
- No reliable data about intervention effect on prescribing
- Imprecise case definition (colonization *versus* infection, reproducibility)
- Other infection control measures
- Changes in length of stay, bed occupancy, staffing levels
## Low Risk of Bias

<table>
<thead>
<tr>
<th>Setting</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematology unit</td>
<td>Cephalosporin restriction</td>
<td>VRE</td>
<td>Bradley 1999</td>
</tr>
<tr>
<td>Whole hospital</td>
<td>Cephalosporin restriction</td>
<td>C difficile, gram-ves</td>
<td>Carling 2003</td>
</tr>
<tr>
<td>NICU</td>
<td>Pen + tobra vs Amox + cefotax</td>
<td>Multiresistant gram-ves</td>
<td>De Man 2001</td>
</tr>
<tr>
<td>ICU</td>
<td>Shorten duration</td>
<td>All resistant bacteria</td>
<td>Singh 2000</td>
</tr>
<tr>
<td>NICU</td>
<td>Antibiotic cycling</td>
<td>Multiresistant gram-ves</td>
<td>Toltzis 2002</td>
</tr>
</tbody>
</table>
Conclusions Microbiology

• 4 low bias studies provide good evidence that prescribing change can improve outcomes
• 11 studies had major threats to validity
• Need more planned interventions with pre-specified post-intervention duration (1 year?)
• Implementing checklist for reporting would help (ORION Sheldon Stone)
Validity: How are we doing?

• Internal
  – Several interventions change prescribing
  – Increasing antibiotic prescribing improves clinical outcome
  – Decreasing antibiotic prescribing improves microbial outcome

• External
  – 4/6 ↑ interventions multi-centre vs 1/60 ↓ interventions
  – No really comparable single hospital studies

• Construct
  – Is increasing antibiotic prescribing harmful?
  – Is reducing antibiotic prescribing harmful?
  – Is choice of antibiotic the best target?
UK MRC Framework for Evaluating Complex Interventions

Continuum of increasing evidence

http://www.mrc.ac.uk/pdf-mrc_cpr.pdf
Implications

• Research
  – Multi-centre Cluster RCTs with embedded time series
  – Clinical and microbial outcomes rule not exception
  – Direct comparison of Education vs Enforcement

• Practice
  – Single hospitals can evaluate interventions with ITS
  – Primary aim is continuous quality improvement
  – Added value:
    • Laying the foundation for definitive research
    • If we all use the same methods we can learn from results in other hospitals

• Policy/ Government
  – No indicators allowed until you fund the necessary research!