Antibiotic bundle: A new reality

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Antibiotic bundle: Is it a new reality?

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Abstract
Probably not
What is a bundle?

- A bundle is a structured way of improving processes of care and patient outcomes.
- It is a straightforward set of practices (usually 3 to 5), that when grouped and implemented together and instituted over a specific time frame, promote best outcomes with a greater impact than if performed individually.
- Anyone in any clinical setting can use the bundle.
What is a bundle?

- Evidence based (best) practice
- All or nothing approach
- All elements crucial: if one element left out process likely to fail
- Elements must be rigorous with straightforward Yes/No answers
- All measurable in one time and space
What are the types of bundles in ID?

- Central venous catheters insertion and maintenance care
- Catheter associated urinary tract infections
- Peripheral vascular catheter care
- Surgical site infection prevention
- Clostridium difficile infection care
- Ventilator associated pneumonia
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CVC-infections prevention bundle

- maximal barrier precautions upon insertion of the catheter
- use of chlorhexidine skin antisepsis
- optimal catheter site selection with subclavian vein as the preferred site for non-tunneled catheters
- hand hygiene measures before insertion
- proper asepsis with catheter care
- daily review of line necessity with prompt removal of unnecessary central lines
Box 1 | Care bundles used to reduce in-hospital mortality
- Central venous catheter/line asepsis
- Diarrhoea and vomiting
- Stroke
- Ventilator acquired pneumonia
- Meticillin resistant *Staphylococcus aureus* infections
- Heart failure
- Surgical site infections
- Chronic obstructive pulmonary disease

Box 2 | Targeted diagnoses from Clinical Classification System
- Peritonitis and intestinal abscess
- Senility and organic mental disorders
- Pleurisy pneumothorax pulmonary collapse
- Aspiration pneumonitis food/vomitus
- Skin and subcutaneous tissue infections
- Acute bronchitis
- Urinary tract infections
- Acute cerebrovascular disease
- Other gastrointestinal disorders
- Septicaemia (except in labour)
- Pneumonia
- Chronic obstructive pulmonary disease and bronchiectasis
- Congestive heart failure non-hypertensive

Fig 2: Hospital standardised mortality ratios (HSMRs) for North West London Hospitals NHS Trust and England, using 2007-8 reference baseline (England=100); bars indicate 95% confidence intervals

Robb, BMJ 2010
**Fig 1** | Hospital standardised mortality ratios (HSMRs) 2006-7 and 2007-8, calculated with 2007-8 national baseline; bars indicate 95% confidence intervals.

**Fig 3** | In-hospital mortality for the 56 diagnoses leading to 80% all deaths. Rising line indicates reducing mortality; X shows the 99% alert level has been reached, indicating a halving of the risk of death. Figures in parentheses show the number of patients involved at each time for calculations starting on 1 April 2006.
Heterogeneity among different bundles targeting the same clinical condition.

Variability in bundle compliance rates and confusion when institutions attempt to benchmark performance.

In addition, while it is maintained that a bundle encompasses a series of "proven" practices, healthcare clinicians need to evaluate the evidence behind the bundle components.

Difficulty in defining reliable and evidence based outcome indicators (surrogate)
Outcomes variables are not always defined uniformly

- Resistance rate
- Recommendations acceptance rate
- Guidelines adherence rates
- Patient satisfaction
- Hospital costs
- Mortality
  - 28-day
  - 60-day
- Infection rate
- LOS
- Duration of antibiotics
- Frequency of antibiotics readministration
- Adverse effects
- Antibiotics expenditures
- Antibiotic exposures
It is recommended that when planning bundle-based care, each aspect be well defined and based on evidence from at least 1 systematic review of multiple well-designed randomized controlled trials (RCT) or on data from at least 1 well-designed RCT.

Aboelela SW, J Hosp Infect. 2007;6:101-108
Systematic review

- Medline, Cochrane database 10 years (2000-2010)

- Inclusion criteria:
  
  Setting: ICU
  Study design: national or international guidelines, RCTs, CCTs, systematic review, controlled before-after study, consensus conference, expert opinion

  Population: Adult patients (>18 yo)
  Intervention: empiric ATB for suspected bacterial infection

- No restriction of language

Tacconelli, ICAAC 2011
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform cultures before starting antibiotics (4/5)</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>≥ 2 blood cultures, 1 from each vascular access (2/5)</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>Starting antibiotics as soon as possible (3/5)</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>Starting antibiotics within 1 hour for septic shock (1/5)</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>Initial empirical antibiotic therapy should cover likely pathogen with good penetration into presumed source</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>Anatomic site of infection established as rapidly as possible (2/5)</td>
<td>strong</td>
<td>very low</td>
</tr>
<tr>
<td>Anatomic site of infection established within 6 h of presentation (1/5)</td>
<td>strong</td>
<td>very low</td>
</tr>
<tr>
<td>Evaluate patients for a focus of infection amenable to source control measures (1/5)</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>Combination empiric therapy in neutropenic patients (1/5)</td>
<td>weak</td>
<td>very low</td>
</tr>
<tr>
<td>De-escalation therapy as soon as cultures are available (4/5)</td>
<td>weak</td>
<td>very low</td>
</tr>
<tr>
<td>Discontinuation of therapy if diagnostic tests negative (4/5)</td>
<td>strong</td>
<td>very low</td>
</tr>
<tr>
<td>Remove vascular catheter if potential infected (2/5)</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>Reassess AT daily to reduce toxicity (2/5)</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>Chest X ray if patient is ventilated (3/5)</td>
<td>strong</td>
<td>low</td>
</tr>
</tbody>
</table>
Major pitfalls of available evidence on the efficacy of antibiotic stewardship

- Mostly limited to uncontrolled before-after studies in a single center
- Outcome measures not well defined
- Heterogeneity of interventions
- Short study duration
- Lack of evaluation of clinical outcomes and adverse effects
- Low quality of study design
- Adherence to infection control measures not controlled

Tacconelli, Curr Op Infect Dis 2010
Survey questionnaire on antibiotic usage in ICU

32-point questionnaire
35 ICUs
- 83% university hospitals
- 10% governamental hospital
- 7% community hospital
- ICU number of bed: 20 (5-88)
- ICU format: closed (83%)

Surgical 31%
Medical 11%
Mixed 51%

Rate of meticillin-resistance among all S. aureus positive blood cultures

<table>
<thead>
<tr>
<th>Percentage</th>
<th>0-5%</th>
<th>6-10%</th>
<th>11-25%</th>
<th>26-50%</th>
<th>&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>42%</td>
<td>17%</td>
<td>20%</td>
<td>9%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

Tacconelli, ICAAC 2011
Do you follow any guideline(s) for empirical antibiotic therapy?

YES, 91%
ATB start..

* Septic shock

PCT 71%
CRP 85%

BAL 37%
Urine cultures 54%
Infection markers 60%
Start within 4 hrs* 89%
Blood cultures 94%

Tacconelli, ICAAC 2011
After starting ATB..

- Infection markers: 60%
- Daily reassessment: 77%
- De-escalation: 94%

Tacconelli, ICAAC 2011
Antibiotic stewardship programme (ABS)

ABC: antibiotic

Tacconelli, ICAAC 2011
Proposed antimicrobial care bundle comprises of six elements:

**On initiation of prescription:**
1. Clinical rationale for initiation
2. Appropriate specimens sent for microbiology culture and sensitivity
3. Adherence to local prescribing guidelines
4. Additional clinical interventions to manage infection (e.g. remove indwelling device, surgical procedure)

**On continuation of prescription:**
5. Daily review based on clinical response and laboratory results regards:
   - De-escalation of treatment
   - Intravenous → Oral switch
   - Stopping antimicrobials
6. Correct performance of therapeutic drug monitoring
# Published antibiotic bundles

<table>
<thead>
<tr>
<th>Bundle</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulcini et al. 2008</strong>&lt;br&gt;After 3 days of therapy:&lt;br&gt;• Was there an antibiotic plan (name, dose, route, interval of administration and planned duration)?&lt;br&gt;• Was there a review of the diagnosis?&lt;br&gt;• If positive microbiological results were available, was there any adaptation of the antibiotic treatment, for example streamlining or discontinuation?&lt;br&gt;• If the patient was initially started on intravenous (IV) antibiotic therapy, was the possibility of IV–oral switch documented?</td>
<td>The inter-rater agreement was &gt; or = 80% for all measures. Data collection was feasible and was easily sustained over several weeks.</td>
</tr>
<tr>
<td><strong>Toth et al 2010</strong>&lt;br&gt;• Documentation of treatment rationale&lt;br&gt;• Collection of appropriate culture specimens according to institutional and national guidelines&lt;br&gt;• Appropriate empirical selection of antibiotics according to institutional and national guidelines at initiation of antibiotic therapy&lt;br&gt;• De-escalation&lt;br&gt;• Selection of appropriate agents for definitive therapy during antimicrobial therapy</td>
<td>Compliance with all quality indicators rose from 16% to 43% (p &lt; 0.001) from the pre-intervention to the intervention period.</td>
</tr>
</tbody>
</table>
Intervention designed to improve the documentation of the reassessment of antibiotic therapies in ICU around day 3 of treatment

- was there an antibiotic plan (name, dose, route, interval of administration and planned duration)?
- was the diagnosis re-evaluated?
- if positive microbiological results were available, was there any adaptation of the antibiotic treatment, for example streamlining or discontinuation?
- if the patient was initially started on IV antibiotic therapy, was the possibility of IV to oral switch documented?
Intervention designed to improve the documentation of the reassessment of antibiotic therapies in ICU around day 3 of treatment.

Table 2

<table>
<thead>
<tr>
<th>Ward and outcome</th>
<th>Baseline level$^a$</th>
<th>Initial trend$^a$</th>
<th>$P$ value</th>
<th>Change in level after the intervention$^a$</th>
<th>$P$ value</th>
<th>Change in trend after the intervention$^a$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation</td>
<td>0.58 (0.45, 0.70)</td>
<td>-0.03</td>
<td>0.18</td>
<td>0.20</td>
<td>0.03</td>
<td>0.05</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>(-0.07, 0.02)</td>
<td></td>
<td></td>
<td>(0.06, 0.35)</td>
<td></td>
<td>(-0.02, 0.12)</td>
<td></td>
</tr>
<tr>
<td>Appropriateness</td>
<td>0.44 (0.31, 0.57)</td>
<td>0.002</td>
<td>0.88</td>
<td>-0.14</td>
<td>0.72</td>
<td>-0.0004</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>(-0.02, 0.03)</td>
<td></td>
<td></td>
<td>(-0.30, 0.02)</td>
<td></td>
<td>(-0.04, 0.03)</td>
<td></td>
</tr>
</tbody>
</table>

95% confidence intervals are given in parentheses.

$^a$ In units of 14-day prescriptions.
Intervention designed to improve the documentation of the reassessment of antibiotic therapies in ICU around day 3 of treatment.

Table 4
Inter-rater reliability for documentation of antibiotic therapy reassessment in medical records.
Concordance inter-évaluateur pour la documentation de la réévaluation des antibiothérapies dans les dossiers médicaux.

<table>
<thead>
<tr>
<th></th>
<th>Observed agreement (%)</th>
<th>Expected agreement %</th>
<th>Kappa (95% confidence interval)</th>
<th>Positive agreement $P_{pos}$</th>
<th>Negative agreement $P_{neg}$</th>
<th>Bias adjusted kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic plan</td>
<td>26/30 (86.7)</td>
<td>60.9</td>
<td>0.66 (0.39–1.07)</td>
<td>0.75</td>
<td>0.91</td>
<td>0.66</td>
</tr>
<tr>
<td>Reviewing the diagnosis</td>
<td>26/30 (86.7)</td>
<td>51.0</td>
<td>0.73 (0.23–1.09)</td>
<td>0.89</td>
<td>0.83</td>
<td>0.72</td>
</tr>
<tr>
<td>Adaptation to microbiological results</td>
<td>30/30 (100)</td>
<td>50.2</td>
<td>1.00 (1.00–1.00)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>IV-PO switch documentation</td>
<td>26/30 (86.7)</td>
<td>60.9</td>
<td>0.66 (0.23–1.09)</td>
<td>0.75</td>
<td>0.91</td>
<td>0.66</td>
</tr>
<tr>
<td>Day 3 bundle</td>
<td>26/30 (86.7)</td>
<td>60.9</td>
<td>0.66 (0.23–1.09)</td>
<td>0.75</td>
<td>0.91</td>
<td>0.66</td>
</tr>
</tbody>
</table>
Intervention designed to improve the documentation of the reassessment of antibiotic therapies in ICU around day 3 of treatment.
http://www.eu-implement.info/ (Kaiser et al, Infection 2011)
2010 Funded DG Sanco / Supervised by the EAHC
Work packages

- WP1: coordination
- WP4: CVC-BSI
- WP2: Dissemination
- WP5: VAP
- WP3: Evaluation
- WP6: Antibiotic therapy
- WP7: Implementation
- WP8: stat. analysis

Development of Antimicrobial Prescribing Care Bundles to Monitor Quality of Antimicrobial Management
WP6
Work description

1. To identify evidence-based recommendations and tools to drive ATB use in ICU and their applicability in daily clinical practice

   - Systematic review of the literature
   - Questionnaire to European ICUs

2. To develop a set of high level of evidence and measurable recommendations for ICU antibiotic prescription

   - Experts’ consensus on ABC-bundle

3. To assess applicability in a specific sample of ICU adult patient

   - Pilot study
     Mar 2011 to Feb 2012
Experts consensus

- two round RAND-modified Delphi-method;

- multidisciplinary 11-member expert panel from 6 European countries (selected through ESCMID SG and ESICM);

- 5 Intensivists, 2 Infectious Diseases, 2 Medical Microbiology, 1 Infection Control, 1 Public Health officer;
Indicators

- **RELEVANCE**
  
  Every indicator was considered “relevant” if the median score for relevance was ≥ 8 and if consensus was reached (i.e. ≥70% of respondents in the 7/8/9 category).

- **PRIORITY**
  
  Selecting the ‘top 3’ recommendations considered most important to assess the quality of antibiotic therapy at the ICU; The ones NEVER selected were excluded.

- **MANDATORY INCLUSION**
  
  To judge whether a recommendation -in personal opinion- should be part of the CARE BUNDLE for good quality of antibiotic therapy at the ICU; 50% respondents with preference for mandatory inclusion.
## 5-Day antibiotic-care bundle

<table>
<thead>
<tr>
<th>1st</th>
<th>the clinical rationale for antibiotic start to be documented in the medical chart at the start of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>appropriate microbiological culture according to local and/or international guidelines should be collected</td>
</tr>
<tr>
<td></td>
<td>the choice of empirical antibiotic therapy should be performed according to local / international guidelines</td>
</tr>
<tr>
<td>2nd</td>
<td>review of the diagnosis based on newly acquired microbiological cultures</td>
</tr>
<tr>
<td></td>
<td>de-escalation therapy (the narrowest spectrum as possible) according to available microbiological results</td>
</tr>
<tr>
<td>3rd-5th</td>
<td>review of the diagnosis based on newly acquired microbiological cultures</td>
</tr>
<tr>
<td></td>
<td>de-escalation therapy (the narrowest spectrum as possible) according to available microbiological results</td>
</tr>
<tr>
<td></td>
<td>interruption of treatment should be considered according to local and/or international guidelines</td>
</tr>
</tbody>
</table>
Prospective observational pilot study

- To measure: adherence, reliability, opportunity for improvement and case mix stability to the elements of the bundle
- Mar 2011 to Feb 2012; 18-bed mixed Italian ICU
- Daily review of patients’ charts
- Data collection from admission sheets, medical and nursing records, medication charts and microbiological and radiological testing reports
### Pilot study

#### Main characteristics

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>186</td>
</tr>
<tr>
<td>Antibiotic courses, n</td>
<td>236</td>
</tr>
<tr>
<td>Total antibiotic days, n</td>
<td>1,048</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>62.2 (19-88)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>112 (60.2%)</td>
</tr>
<tr>
<td>SAPS II, mean (range)</td>
<td>49.0 (15-105)</td>
</tr>
<tr>
<td>ICU admission for</td>
<td></td>
</tr>
<tr>
<td>respiratory failure, n (%)</td>
<td>83 (35.1)</td>
</tr>
<tr>
<td>septic shock, n (%)</td>
<td>50 (21.1)</td>
</tr>
<tr>
<td>neurological illness, n (%)</td>
<td>42 (17.8)</td>
</tr>
<tr>
<td>trauma, n (%)</td>
<td>37 (15.6)</td>
</tr>
<tr>
<td>cardiovascular failure, n (%)</td>
<td>13 (5.5)</td>
</tr>
<tr>
<td>surgery, n (%)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>other, n (%)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Length of ICU stay, mean (SD)</td>
<td>4.9 (7)</td>
</tr>
<tr>
<td>Length of antibiotic therapy, mean (SD)</td>
<td>9 (7.7)</td>
</tr>
<tr>
<td>Underlying illness</td>
<td></td>
</tr>
<tr>
<td>cardiovascular, n (%)</td>
<td>83 (44.6)</td>
</tr>
<tr>
<td>lung, n (%)</td>
<td>42 (22.5)</td>
</tr>
<tr>
<td>brain, n (%)</td>
<td>41 (22)</td>
</tr>
<tr>
<td>diabetes</td>
<td>34 (18.2)</td>
</tr>
<tr>
<td>neoplasm, n (%)</td>
<td>29 (15.5)</td>
</tr>
<tr>
<td>blood, n (%)</td>
<td>25 (13.4)</td>
</tr>
<tr>
<td>abdominal, n (%)</td>
<td>25 (13.4)</td>
</tr>
</tbody>
</table>
Slide withheld at request of author
Online Lecture Library

Slide withheld at request of author
Bundle applicability

- **Reliability:**
  - a sample of records was collected by 2 independent data reviewers and percentage of agreement measured in Cohen k coefficient
  - acceptable reliability (k>0.4) for all indicators but “clinical rational for antibiotic start documented in the medical chart”

- **Opportunity for improvement (< 85%)** for the majority of the indicators.

- **Case mix stability:**
  - Distribution of outcome was analysed according to age, sex and SAPS II score.
  - Stable distributions of all indicators over the 3 variables.
Conclusions

- Evidence that documentation of the details of patients receiving antibiotic is suboptimal
- Evidence that many clinicians find hard to descale or discontinue antibiotic therapy
- The antibiotic bundle could be considered the minimum requirement and should be the pillar of any antibiotic stewardship programme
- Side effects need to be evaluated
- Feedback and audit to be planned previously
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Dreams are my reality.....

- Atb bundle could/should:
  - Reduce inappropriate starting of therapy
  - Reduce duration of therapy
  - Reduce side effects
  - Reduce Clostridium difficile
  - Reduce rate of atb resistance
  - Society benefit
Conclusions

- There is an urgent need for an agreement on the principles and key components of ABS at international level (role for bundle?)
- There is a need for further research on the comparative effectiveness and cost-effectiveness of ABS strategies and interventions in different healthcare settings
- Global stewardship collaboration and an Antibiotic Stewardship Assessment tool kit to assess the maturity of ABS
- This work could form a fledgling collaboration between all the stewardship organisations within national and international ID and CM societies
Antibiotic bundle: Is it a new reality, isn’t it? Nope

Antibiotic bundle: Do we need it, don’t we? Yope!