Strategies to control antibiotic resistance (low- and middle-income countries)

Prof. Stephan Harbarth, MD MS
Email: stephan.harbarth@hcuge.ch
Service de Prévention et Contrôle de l’Infection

Hôpitaux Universitaires de Genève

NDM1 and Pan-Resistance

Global Spread NDM1

Note: recent cases travel related not medical tourism

OUTLINE

Hospital setting
- Strategic priorities
- Antibiotic control policies

Ambulatory setting
- Macro-level determinants
- Country examples of successful changes

Improve antibiotic use
- Monitor and provide feedback on occurrence of AMR
Control programs for multiresistant Staphylococcus aureus (MRSA)

<table>
<thead>
<tr>
<th>Region</th>
<th>Proportion of MRSA among all S aureus isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>25/43 (58%)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>13/27 (48%)</td>
</tr>
<tr>
<td>Africa</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>USA</td>
<td>1/5 (20%)</td>
</tr>
<tr>
<td>South America</td>
<td>4/6 (67%)</td>
</tr>
</tbody>
</table>

Richet et al. Infect Control Hospital Epi 2003; 24: 334-341

The important role of sentinel hospitals

- Centralization of available laboratory resources in a few selected centers
- Monitoring and reporting of AB susceptibility data (WHO.net)
- Adapt empiric treatment regimens


Improve antibiotic use

- Monitor and provide feedback on occurrence and impact of AMR
- Optimize choice and duration of empiric antimicrobial therapy

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Survival Among 401 Patients with Nosocomial Pneumonia Assigned to Short (8 d) or Long (15 d) Antimicrobial Treatment

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Emergence of multiresistant pathogens for patients who had pulmonary infection recurrence

42.1% 62.3%

P = 0.04


BMJ Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial

Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months (Review)

Haider RA, Saeed MA, Bhutta ZA
Non-severe CAP in children - Conclusions of recent review -

- Most episodes of pneumonia can be treated for a short duration
- Ambulatory non-severe pneumonia can be treated with 3 d of oral antibiotics
- Shorter course results in lower prevalence of resistant organisms


Reduced antimicrobial R

- 5 vs 10 days (Schrag et al JAMA 2001)
- S. pneumoniae 34% vs 44%
- H. influenzae 57% vs 61%

- 3 vs 5 days (ISCAP BMJ 2004)
- S. pneumoniae 67% vs 78%
- H. influenzae 54% vs 62%

- 3 vs 5 days (SCC WHO report 2003)
- S. pneumoniae 62% vs 64%

Improve antibiotic use

- Monitor and provide feedback on occurrence of AMR
- Optimize choice and duration of empiric antimicrobial therapy
- Optimize perioperative antimicrobial prophylaxis

Antibiotic Prophylaxis and the Risk of Surgical Site Infections following Total Hip Arthroplasty: Timely Administration Is the Most Important Factor


Common Misconceptions in Surgical Prophylaxis

- Broad-spectrum is better
- Longer antibiotic prophylaxis is better
- Prophylaxis should be continued until all “tubes” are out

Misuse of prophylactic antibiotics in a university hospital, China

80% of prophylactic antibiotics (191/239) were started after the end of the operation

Overuse of prophylactic antibiotics in a community hospital, Saudi Arabia -- representative cases --

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Prophylactic antibiotics administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery</td>
<td>Ampicillin, amikacin, cefotaxime</td>
</tr>
<tr>
<td>Urinary cath</td>
<td>Amoxyllin, metronidazole</td>
</tr>
<tr>
<td>C-section</td>
<td>Cephradine, ceftriaxone, gentamicin, metronidazole</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>Cephradine, cefoxitin, amikacin, metronidazole, TMP-SMX</td>
</tr>
<tr>
<td>Cystoscopy</td>
<td>Amikacin, tetracycline, cefazidime, amoxyllin-clav</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>Cephradine, cefuroxime, gentamicin</td>
</tr>
<tr>
<td>Incision</td>
<td>Ampicillin, amikacin, amoxyllin-clav</td>
</tr>
<tr>
<td>Episiotomy</td>
<td>Amoxyllin, gentamicin, cephradine, metronidazole</td>
</tr>
<tr>
<td>Delivery</td>
<td>Amoxyllin, gentamicin, cephradine, metronidazole</td>
</tr>
</tbody>
</table>


Duration of surgical prophylaxis and selection of resistance

<table>
<thead>
<tr>
<th>Cardiovascular surgery</th>
<th>n=2,641, multivariate analysis</th>
<th>OR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 48 h prophylaxis</td>
<td>&gt; 48 h prophylaxis</td>
<td>1.0 (0.8-1.3)</td>
<td>ns</td>
</tr>
<tr>
<td>SSI</td>
<td>Resistant</td>
<td>1.7 (1.1-2.7)</td>
<td>0.027</td>
</tr>
<tr>
<td>Enterobacteriaceae/enterococci</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Improve perioperative antibiotic prophylaxis (ABP)

<table>
<thead>
<tr>
<th>Process</th>
<th>Problem area</th>
<th>System changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP choice</td>
<td>Suboptimal</td>
<td>Guidelines</td>
</tr>
<tr>
<td></td>
<td>Coverage too large</td>
<td>Adequate supply</td>
</tr>
<tr>
<td>adequate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing correct</td>
<td>Too early or too late</td>
<td>Administrator in preoperative area</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Designate responsible person</td>
</tr>
</tbody>
</table>


Prophylactic Antibiotics and Infections after Cesarean Section in Colombia

Antibiotic prophylaxis in C-section

- Appropriate indication
- Agent, dose, # of doses
- Timing of first dose


Use and timing of perioperative antibiotics and surgical site infection rates

Weinberg et al. Arch Intern Med 2001; 161:2357-65

Improve antibiotic use (2)

- Decrease diagnostic uncertainty:
- Improve diagnostic tools
- Promote use of clinical algorithms

Weinberg et al. Arch Intern Med 2001; 161:2357-65

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Antibiotic treatment without microbiologic cultures in China (Hospital) and Nepal (ICU)

Shankar et al. Infect Control 2003; 31: 410-14


Use of clinical algorithms

- Prediction of bacteremia & mortality in hospitalized Malawian children
- Association with lethargy, oral thrush, chronic cough and malnutrition
- The WHO Young Infants Study Group
- Clinical prediction rule to identify and treat serious bacterial infection


Antibiotic prescriptions in lower respiratory tract infection comparing standard group and PCT-guided group

Harbarth, SPCI-HUG Christ-Crain M et al. Lancet 2004

Procalcitonin: a long & complicated story...

Schrumpf et al. Schweiz Med Wochenschr 2009; 139: 318-26


Antibiotic prescription (%)

p = 0.03 p = 0.003 p < 0.001 p < 0.001 p = 0.003

ProRATA

Lancet 2010

Use of Procalcitonin to Shorten Antibiotic Exposure in ICU Patients: The ProRata Trial

Bouadma et al. Lancet 2010


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Use of Procalcitonin to Shorten Antibiotic Exposure in ICU Patients: The ProRata Trial

OR at D28; 0.81, 90% CI 0.63-1.29
OR at D60; 1.09, 90% CI 0.79-1.51

Probability of Survival, %

Days after Inclusion

Control group
Procalcitonin

Impact of an antibiotic restriction policy on hospital expenditures and bacterial susceptibilities: a lesson from a pediatric institution in a developing country

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vials (#)</td>
<td>199,427</td>
<td>132,496</td>
</tr>
<tr>
<td>Total costs ($)</td>
<td>699,543</td>
<td>347,261</td>
</tr>
</tbody>
</table>

-- Stable or decreasing resistance rates --

Gross PA et al. Med Care 2001; 39: Suppl 55-69

Does restriction always work?

Formulary restriction at Mass Gen Hosp, Boston (USA):
“Imipenem, tic/clav, aztreonam, cefta, cipro, pip/tazo require prior approval by infectious diseases”

The reality at the same hospital....
35-y old woman with severe sepsis:
“Ampicillin-sulb, clindamycin, penicillin, gentamicin, vancomycin were infused intravenously”


Improve antibiotic use (2)

- Decrease diagnostic uncertainty
- Implement formulary restrictions for important types of antimicrobial use
- Improve diagnostic tools
- Implement formulary restrictions for important types of antimicrobial use
- Improve antimicrobial prescribing:
  - Education (pre- and postgraduate)
  - Practice guidelines
  - Administrative means (antibiotic order forms)
  - Feedback to prescribers

Implementing practice guidelines for appropriate AB use: Systematic review

- 40 studies (in- and outpatient areas)
- Multifaceted implementation methods were most successful
- Most useful implementation methods:
  - Locally adapted guidelines (drug committee)
  - Small-group interactive sessions
  - Academic detailing
  - Participation of opinion leaders
  - Feedback to prescribers
Impact of an educational program on antibiotic use in a tertiary care hospital in Thailand

Appropriate antibiotic use (in-patients, %)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preintervention period</th>
<th>Postintervention period</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate antibiotic use</td>
<td>1906 (43)</td>
<td>968 (25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Reason for inappropriateness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate surgical prophylaxis</td>
<td>452 (25)</td>
<td>116 (10)</td>
<td>.01</td>
</tr>
<tr>
<td>Use of antibiotic without any evidence of infection</td>
<td>723 (43)</td>
<td>206 (25)</td>
<td>.04</td>
</tr>
<tr>
<td>Redundant spectrum</td>
<td>217 (12)</td>
<td>50 (11)</td>
<td>.03</td>
</tr>
<tr>
<td>Bacterial resistance</td>
<td>236 (13)</td>
<td>99 (19)</td>
<td>.07</td>
</tr>
<tr>
<td>Narrow spectrum was available</td>
<td>161 (10)</td>
<td>41 (15)</td>
<td>.04</td>
</tr>
<tr>
<td>Department</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>473 (35)</td>
<td>170 (30)</td>
<td>.01</td>
</tr>
<tr>
<td>Obstetrics and gynecology</td>
<td>452 (25)</td>
<td>126 (22)</td>
<td>.17</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>436 (23)</td>
<td>113 (20)</td>
<td>.14</td>
</tr>
<tr>
<td>Other</td>
<td>307 (17)</td>
<td>113 (20)</td>
<td>.12</td>
</tr>
</tbody>
</table>


Impact of an educational program on antibiotic use in a tertiary care hospital in Thailand

Antibiotic resistance

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Preintervention period</th>
<th>Postintervention period</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-resistant Staphylococcus aureus</td>
<td>48</td>
<td>33.5</td>
<td></td>
</tr>
<tr>
<td>ESBL-producing Escherichia coli</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>ESBL-producing Klebsiella pneumoniae</td>
<td>33</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Third-generation cephalosporin-resistant Acinetobacter baumannii</td>
<td>30</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Imipenem-resistant Pseudomonas aeruginosa</td>
<td>27</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Multi-drug-resistant Acinetobacter baumannii</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>


Interventions to improve quality of antibiotic prescribing for hospital inpatients (review)


- 51/66 studies showed a significant improvement in at least one outcome
- Reduction of costs, AMR or HCAI
- Interventions to improve antibiotic prescribing in inpatients likely to be successful
- Absence of good evidence which interventions are most cost-effective in reducing AMR


Outpatient setting

Macro-level determinants

Macro-level determinants influencing antibiotic overuse in the outpatient setting

Prescriber factors

Patient factors

Cultural influences

Social determinants

Regulatory practices

Antibiotic overuse & misuse

Antibiotic-resistant microorganism

Improving antibiotic use in low-income countries: an overview of evidence on determinants

Aryanti Radyowijati, Hilbrand Haak. Consultancy for Health and Development, Siibaromi 7, 2517 HV Leiden, The Netherlands

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Index of antibiotic demand
- Cumulative proportion of patients expecting antibiotics for RTI --

Compliance Varies by Country

Turkey France Spain UK Belgium Italy

Branthwaite & Pechere; J Intern Med Research 1996; 24: 229-238

Compliance Varies by Country

UK 90%
Fr 82%
Bel 82%
Sp 62%
M 74%
Ita 65/89%
Sp 55%
UK 42%
Ma 47%
Br 79%
Ita 41%
Ch 37%
Bra 26%
Tha 22%
Jap 66%
Mex 74%
USA 80%
SA 82%
Bra 78%
Phil 74%
NL 90%

Study 3: Data on file. Pfizer Inc.

Available in a pharmacy in Delhi – over-the-counter without prescription!

Country examples: Possible interventions

Public campaigns with the aim to decrease antibiotic misuse in Europe

Outcome regarding antibiotic use

Huttner B. et al. Lancet Infect Dis 2010

Huttner B. et al. Lancet Infect Dis 2010
**Action plan**

- In 1999, Chile decided an intervention to:
  - educate physicians & public
  - regulate the consumption of antibiotics
  - restrict over-the-counter antibiotic sales
South Korea: Impact of the Policy on Prescribing

Korea- Government Policy
- A new Korean government policy announced in 2000 prohibited doctors from dispensing and pharmacists from prescribing drugs by law.

South Korea: Impact of the Policy on Prescribing

Result 1: MTP at General Teaching Hospitals
Problem: Pre- and post-surgery ABs in elective hernia surgery
Indicator: % patients receiving antibiotics

Result 2: MTP at Public Hospitals
Problem: Overuse of AB in acute diarrhoea (Siemen)
- Pre- and post-surgery ABs in Caesarian surgery (Yogy)
Indicator: % patients receiving antibiotics

ANTIBIOTIC USE OVER TIME

Notes: In parallel of the activity to reduced the use of antibiotic in ARI, all HCs also used the MTP approach to address the other problems in medicine use.
Policy priorities: AB use

Local level
- Improve perioperative prophylaxis
- Promote short-course, high-dose AB therapy
- Decrease diagnostic uncertainty by any type of diagnostic tools or decision support
- Promote local guidelines and drug committees

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Policy priorities: AB use

National level
- Create sentinel laboratories for surveillance of antibiotic resistance
- Change consumer expectations
- Implement healthcare regulation for the prudent use of antibiotics
- Control marketing activities of industry

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Summary of Measures

<table>
<thead>
<tr>
<th>Ressources</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measures</td>
<td>Improve antibiotic prophylaxis, Clinical algorithms</td>
<td>Surveillance, Microbiologic support, Restriction &amp; education, Decision support systems, New diagnostic markers, Academic detailing</td>
<td></td>
</tr>
</tbody>
</table>

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“The development of new antibiotics without having mechanisms to insure their appropriate use is much like supplying your alcoholic patients with a finer brandy.”

Dennis Maki 1998

Third International Conference for Improving Use of Medicines
Bibliotheca Alexandrina, Alexandria, Egypt - April 10 - 14, 2011
Informed Strategies, Effective Policies, Lasting Solutions

Abstracts will need to be submitted before Dec 5th 2011

WHO Webinar