Antimicrobial Resistance
The Healthcare Professional Perspective
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NDM1 and Pan-Resistance

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Summary

Background: Emergence of Enterobacteriaceae with resistance to colistin-requiring New Delhi metallo-β-lactamase (NDM-1) is a potential new global health problem. We investigated (re-emergence of NDM-1) in outpatient and inpatient settings in India, Pakistan, and the UK.

Methods: Enterobacteriaceae isolates were collected from two major cities in India—Chennai (south India) and Bhubaneswar (east India)—and three cities in the UK—Bristol, Oxford, and London. NDM-1 susceptibility was assessed by three methods: (i) direct testing, (ii) colistin penetration assay, and (iii) colistin–β-lactamase resistance test. Data were collected from January 2003 to November 2010.

Results: We isolated 44 isolates with NDM-1 in Chennai. In Bhubaneswar, 37 isolates with NDM-1 were isolated from India and Pakistan. NDM-1 is more frequent among Enterobacter aerogenes (52%) and Klebsiella pneumoniae (16%), which were highly resistant to all antibiotics except to tigecycline and colistin. NDM-1 isolates from India and Pakistan were isolated from patients of both UK and US origin. The number of NDM-1 isolates increased from 2003 to 2010, with the highest incidence in 2007–2008, followed by a decline in 2010.

Conclusions: The potential of NDM-1 to evolve highly virulent strains is great, and effective local and national surveillance is needed.

Global Spread NDM1

Note: recent cases travel related not medical tourism

Courtesy: J. Conly, Geneva
Good times of antibiotics have passed

Antimicrobial resistance… Who is responsible?

Globalisation

Dr Z

Patient Y

The bacteria itself

Food processing industry
Antibiotic dilemma

Benefit is individual

Risk is collective

OUTLINE

- Hospital setting
  - Strategic priorities
  - Antibiotic control policies

- Ambulatory setting
  - Macro-level determinants
  - Country examples of successful changes
L’acteur contracte un staphylocoque à la jambe droite. Ne supportant plus la douleur, il choisit l’amputation.
Improve antibiotic use

- Monitor and provide feedback on occurrence of AMR

Control programs for multiresistant \textit{Staphylococcus aureus} (MRSA)

<table>
<thead>
<tr>
<th>Region</th>
<th>Able to calculate the proportion of MRSA among all \textit{S. aureus} isolates</th>
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<tbody>
<tr>
<td>Western Europe</td>
<td>25/43 (58%)</td>
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<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
- Adapt empiric treatment regimens

Archibald LK & Reller LB. Clinical Microbiology in Developing Countries. Emerg Infect Dis 2001; 7: 302-305

Improve antibiotic use

- Monitor and provide feedback on occurrence and impact of AMR
- Optimize choice and duration of empiric antimicrobial therapy
Survival Among 401 Patients with Nosocomial Pneumonia Assigned to Short (8 d) or Long (15 d) Antimicrobial Treatment

Emergence of multiresistant pathogens for patients who had pulmonary infection recurrence
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

**Improve antibiotic use**

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

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**Common Misconceptions in Surgical Prophylaxis**

- Broad-spectrum is better
- Longer antibiotic prophylaxis is better
- Prophylaxis should be continued until all “tubes” are out
Antibiotic Prophylaxis and the Risk of Surgical Site Infections following Total Hip Arthroplasty: Timely Administration Is the Most Important Factor

*Clin Infect Dis* 2007;44(7):921-7

![Graph showing % SSI vs time to incision in minutes](image1)

Misuse of prophylactic antibiotics in a university hospital, China

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

![Graph showing % of duration of perioperative prophylaxis](image2)

## Duration of surgical prophylaxis and selection of resistance

### Cardiovascular surgery

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


### Use and timing of perioperative antibiotics and surgical site infection rates

- **Correct ABP**
- **SSI rate**

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

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

![Bar chart showing antibiotic treatment without microbiologic cultures in China and Nepal. The chart indicates the percentage of patients treated without cultures compared to those treated with cultures. The data from Suping Hu et al. (J Infect 2003; 46:161-63) and Shankar et al. (Am J Infect Control 2003; 31: 410-14).]
Procalcitonin: a long & complicated story…


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

Christ-Crain M et al, Lancet 2004
Use of Procalcitonin to Shorten Antibiotic Exposure in ICU Patients: The ProRata Trial

Bouadma et al. Lancet 2010

**Graph 1:**
- **Y-axis:** Duration of treatment (days)
- **X-axis:** All patients, CAP, VAP, Intraabdominal infection, UTI, Positive blood cultures
- **Data:**
  - Control: 9.9, 10.6, 9.4, 10.8, 14.5, 12.8
  - PCT: 6.1, 5.6, 7.3, 8.1, 7.4, 9.8

**Table:**
- **N:** 314, 307, 101, 79, 20, 14, 18, 24, 53, 55
- **Values:**
  - CAP: 0, 2, 4
  - VAP: 14, 75
  - Intraabdominal infection: 20, 14
  - UTI: 18
  - Positive blood cultures: 24

**Graph 2:**
- **Y-axis:** Probability of survival, %
- **X-axis:** Days after inclusion
- **Data:**
  - Control group
  - Procalcitonin

**Results:**
- OR at D28: 0.81, 90% CI 0.63-1.29
- OR at D60: 1.09, 90% CI 0.79-1.51

Bouadma et al. Lancet 2010
Improve antibiotic use (2)

- Decrease diagnostic uncertainty
- Implement formulary restrictions for important types of antimicrobial use

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)

- 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

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

[Diagram: 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

Harbarth et al, Emerg Infect Dis 2002; 8: 1460-1467
Index of antibiotic demand
- Cumulative proportion of patients expecting antibiotics for RTI --

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

Compliance with antibiotic use varies by country

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

Huttner B. et al. Lancet Infect Dis 2010

Outcomes regarding antibiotic use:

- **1992-1997:** 35% reduction (children)
- **1997-2005:** 9% reduction
- **1997-2007:** About 35% reduction (children 0-5 years)
- **2003-2005:** 10% reduction
- **1999-2007:** 36% reduction
- **2002-2007:** 23% reduction
- **1999-2002:** 15% reduction
- **1999-2003:** Decrease by 0.18 prescriptions/1000 consultations/GP/month.
- **2004-2005:** 6% reduction over winter months compared to control
Action plan

- In 1999, Chile decided an intervention to:
  - educate physicians & public
  - regulate the consumption of antibiotics
  - restrict over-the-counter antibiotic sales
Las Últimas Noticias

MEDIDA SE APLICARÁ A PARTIR DE SEPTIEMBRE

Exigirán receta para comprar antibióticos

Afecta, entre otros, a la amoxicilina y a la eritromicina
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

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

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
Policy priorities: AB use

International level
- Support national and international initiatives
- Coordinate initiatives
- Develop public-private partnerships
- Monitor use and resistance, feedback, act, and regulate

“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