The impact of clinical daily prescribing on antimicrobial resistance

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IF NOT TACKLED, RISING AMR COULD HAVE A DEVASTATING IMPACT

By 2050, the death toll could be a staggering one person every three seconds if AMR is not tackled now.

http://amr-review.org/
The image shows a bar chart illustrating the number of additional infections per year associated with various medical procedures. The chart compares different procedures such as colorectal surgery, Caesarean section, hysterectomy, transrectal prostate biopsy, spinal surgery, surgical abortion, appendectomy, total hip replacements, pacemaker implantation, cancer chemotherapy, and hip fracture surgery. Each bar is color-coded to indicate additional infections for different reduction percentages in efficacy.

- Colorectal surgery: 60,000 additional infections per year
- Caesarean section: 50,000 additional infections per year
- Hysterectomy: 40,000 additional infections per year
- Transrectal prostate biopsy: 30,000 additional infections per year
- Spinal surgery: 20,000 additional infections per year
- Surgical abortion: 10,000 additional infections per year
- Appendectomy: 5,000 additional infections per year
- Total hip replacements: 2,000 additional infections per year
- Pacemaker implantation: 1,000 additional infections per year
- Cancer chemotherapy: 500 additional infections per year
- Hip fracture surgery: 200 additional infections per year

The present situation estimate shows the number of additional infections for a 10%, 30%, 70%, and 100% reduction in efficacy.
The impact of antimicrobial resistance on clinical daily prescribing

The impact of clinical daily prescribing on antimicrobial resistance

Chicken or Egg?
Ideal world

1. No mistake in prescription
2. Resistance fully accounted in prescription
3. Prescription will minimally impact resistance
The percentage of inappropriate empiric antibiotic use ranged from **14% to 79%** (Q1-Q3: 28.1% to 57.8%); 13 of 27 studies (48%) described an incidence of 50% or more.

Effect of appropriate and inappropriate antibiotic therapy against severe infections.
1. Would you accept as a patient to start a chemotherapy or a cardiologic one if your doctor would tell you „You know there is a possibility up to 78% that this therapy is a wrong one..“

2. Would you accept that the engineer that is building up your house would tell you „You know there is a possibility up to 78% that your ceiling is coming down in 2 years?“
Effect of ASPs on hospitalized patients

145 studies / 14 objectives

Guideline-adherent empirical therapy was associated with a RR for mortality of 35% and for de-escalation of 66%

Resistance rates for restricted antibiotics were significantly decreased across a wide variety of infective agent and drug combinations.

A few studies reported increased resistance rates for non-restricted antibiotics.

Significant protective effect on mortality
pooled risk ratio 0.65; 95% CI: 0.54, 0.80

Schuts, LID 2016
A 3-step prospective study was designed

1. Systematic review of literature reporting QIs for antibiotic usage in ICU

2. Develop a bundle including the most relevant QIs through a two round RAND-modified Delphi-method of an experts panel

3. Measure of the adherence to the bundle in 2 mixed University ICU.

- To select the QIs a 9-point Likert scale was applied.
- Indicator was considered “relevant” if the median score was ≥ 8 and if consensus was reached (i.e. ≥70% of respondents in the 7/8/9 category).

Tacconelli, under submission
1190 potentially relevant studies identified and screened for retrieval

85 studies retrieved for more detailed evaluation

70 studies excluded:
- 4 studies not performed in ICU
- 17 studies not concerning empirical ATB
- 3 studies concerning infections due to specific pathogen
- 12 reviews
- 33 observational studies

15 studies included:
- 5 guidelines
- 4 randomized controlled trials
- 6 systematic reviews
Eleven QIs were extracted and sent to the expert group for evaluation.

After three rounds of consultation 6 QIs were classified as “relevant” and were included as recommendation in a 5-day ABC-Bundle.
Rette aNTibiOTika
RETTE LEBEN

1. Übermäßiger Einsatz und unsachgemäßer Gebrauch von Antibiotika ist ein Hauptgrund für Antibiotika-Resistenz
2. Antibiotika-Resistenz und damit verbundene Mortalität steigen weltweit
3. Die Antibiotika-"Pipeline" ist derzeit leer

Kein Patient sollte unnötig Antibiotika bekommen

NOT ist ein Projekt der UKT gegen übermäßigen Gebrauch von Antibiotika
63% reduction in antibiotic usage
33% imipenem
16% quinolones
HOW SURVEILLANCE CAN IMPROVE HEALTH OUTCOMES

Globally
Provide early warnings of emerging threats and data to identify and act on long-term trends

Nationally
Guide policy and ensure appropriate and timely public health interventions

Locally
Allow healthcare professionals to make better informed clinical decisions to ensure better patient outcomes
Does universal active MRSA surveillance influence anti-MRSA antibiotic use?

Figure 2. Evolution of the diagnostic accuracy of (a) initial anti-MRSA therapy for MRSA-positive admission cultures over time and (b) nasal MRSA surveillance for MRSA-positive admission cultures over time.

Jones JAC 2014
Trends in MRSA prevalence in EU countries 2015

Tacconelli & Beryl, DRIVE-AB 2015
Trends BSI due to VSE / MR-CoNS

Graphs by group(country)

Glycopeptide consumption (DDD/1000 patients)
VSEfm prevalence(%) among invasive isolates

Tacconelli & Beryl, DRIVE-AB 2015
Glycopeptide consumption and prevalence of BSI due to MRSA, VSE and CoNS
The largest sex difference in absolute numbers was observed for antibiotics, more commonly dispensed to women.

Loikas, 2014
Overall antibiotics prescription
Age and gender

Tacconelli, JAC 2016
Women were 27% more likely than men to receive an antibiotic prescription in their lifetimes. The amount of antibiotics prescribed to women was 36% higher than that prescribed for men in the 16 to 34 years age group and 40% greater in the 35 to 54 years age group.

<table>
<thead>
<tr>
<th>Antibiotic classes</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>5</td>
<td>1.44 (1.24, 1.65)</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>5</td>
<td>1.32 (1.24, 1.41)</td>
<td></td>
</tr>
<tr>
<td>Penicillins</td>
<td>5</td>
<td>1.21 (1.07, 1.34)</td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>0</td>
<td>1.09 (0.91, 1.28)</td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>5</td>
<td>1.16 (0.98, 1.34)</td>
<td></td>
</tr>
</tbody>
</table>
Women a quarter more likely to be given antibiotics than men sparking concerns 'doling out' prescriptions is fuelling a boom in superbugs

- Women aged 35 to 54 even more likely to receive antibiotics than men
- Drugs with highest gender differences were for respiratory tract infections
- Government is desperate to reduce needless prescriptions for antibiotics

from German journal „Female doctors are prescribing more antibiotics..“

from Italian journal „Female ask more frequently antibiotics because they have to work more and cannot be sick..“
Antibiotics usage impacts on MRSA incidence
76 studies, 24,230 patients

### Antibiotics usage impacts on MRSA incidence

TABLE 3. Incidence of acquisition for 1,000 antibiotic days by antibiotic class, patient risk factor, and duration of therapy for the overall target ARB (i.e., MRSA, VRE, and CR-PA) and specific for MRSA.

<table>
<thead>
<tr>
<th>Antibiotic class and risk factor</th>
<th>Overall</th>
<th>By duration of therapy:</th>
<th>MRSA incidence overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>13.8</td>
<td>18.3</td>
<td>13.2</td>
</tr>
<tr>
<td>Dialysis</td>
<td>26.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>22.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>20.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad-spectrum cephalosporins</td>
<td>5.8</td>
<td>5.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>27.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>17.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>10.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤ 70 yrs</td>
<td>8.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>5.9</td>
<td>6.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Age of &gt;70 yrs</td>
<td>8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>9.2</td>
<td>11.3</td>
<td>8.0</td>
</tr>
<tr>
<td>HIV</td>
<td>19.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>15.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>5.8</td>
<td>7.2</td>
<td>10.9</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>22.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>16.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>6.5</td>
<td>11</td>
<td>3.1</td>
</tr>
<tr>
<td>Age of &gt;70 yrs</td>
<td>16.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Only relevant risk factors are reported.

Tacconelli, Antimicr Agents Chemoth, 2009
Impact of H. pilori combination therapy with clarithromycin and metronidazole on intestinal microbiota

Jakobsson, PLOS One 2013
Long-term ecological impacts of antibiotic administration on the human intestinal microbiota

7 day clindamycin
2 year follow up
4 patients
4 controls

Jernberg, ISME 2007
Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children

142 children
2-7 y.o.
Sampled 2 time

Katri Korpela, Nature Communication 2015
Country-specific antibiotic use practices impact the human gut resistome

Forslund, Genome Res 2013

© by author
Hand Hygiene: strong recommendation

ESBL+Enterobacteriaceae

Tacconelli, CMI 2014
MDR- A.baumannii

Hand Hygiene: strong recommendation

Epidemic

Endemic

Tacconelli, CMI 2014
How we can personalise antibiotic therapy?
Screening samples: 58,804

Nasal  30,482
Rectal  28,322

At Hospital Admission:
- 20,217
- At Hospital Discharge: 13,298
- During Antibiotic treatment: 25,289

Cohort

Positives samples: 2980 (5%)
- 2450 (8.6%) positive samples for ESBL-Ent
- 530 (1.7%) positive samples for MRSA

Tacconelli, ECCMID 2016  www.saturn-project.eu
ESBL colonisation develops in 18% of patients taking cephalosporins (very common AE)

<table>
<thead>
<tr>
<th>Term</th>
<th>Numerical rate</th>
<th>Percentage rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>More than 1 in 10</td>
<td>10% or higher</td>
</tr>
<tr>
<td>Common</td>
<td>1 in 10 – 1 in 100</td>
<td>10% – 1%</td>
</tr>
<tr>
<td>Uncommon</td>
<td>1 in 100 – 1 in 1000</td>
<td>0.1% to 1%</td>
</tr>
<tr>
<td>Rare</td>
<td>1 in 1000 – 1 in 10,000</td>
<td>0.01% to 0.1%</td>
</tr>
<tr>
<td>Very rare</td>
<td>Less than 1 in 10,000</td>
<td>Less than 0.01%</td>
</tr>
</tbody>
</table>

- Rate at hospital admission: 11%
- Rate of acquisition in patients without antibiotic therapy: 9.6%
- Rate of acquisition in patients after antibiotic therapy: 23.5%
- Rate of infections after colonization: 7%

Tacconelli, ECCMID 2016
FDA announces safety labeling changes for fluoroquinolones

[5-12-16] Today, the FDA is requiring labeling changes for antibacterial drugs called fluoroquinolones, including an updated boxed warning, stating that the serious side effects associated with fluoroquinolones generally outweigh the benefits for patients with sinusitis, bronchitis and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

- FDA Response to Citizen Petition: Southern Network on Adverse Reactions (SONAR), Docket No. FDA-2014-P-0856. The Petition requests that FDA require changes in the professional labeling of Levaquin (levofloxacin) regarding “Potential Mitochondrial Toxicity”.
Ranking of β-lactams according to spectrum and ecological impact

- 28 experts from ICU, ID and CM
- Delphi method (4 successive questionnaires)
- More than 70% of similar answers to a question were necessary to reach a consensus.

Unable to differentiate ecological consequences of piperacillin/tazobactam, ticarcillin/clavulanic acid, fourth-generation cephalosporin and antipseudomonal third-generation cephalosporin.

TABLE 3. Consensual ranking of β-lactams according to both their spectrum and their resistance-promoting potential

<table>
<thead>
<tr>
<th>Rank</th>
<th>Molecule(s)</th>
<th>Similar response rate (%)</th>
<th>Consensus reaching round number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amoxicillin</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Amoxicillin + Clavulanic Acid</td>
<td>88</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Third-generation cephalosporin</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Cepheidoxycarbonyl-penicillin</td>
<td>71</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Piperacillin + Tazobactam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ticarcillin + Clavulanic Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Four-generation cephalosporin, Antipseudomonal third-generation cephalosporin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Etapenem</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Imipenem</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>Meropenem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Doripenem</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Indicates the proportion of the Expert Panel members that agreed with the molecules included in each rank of the classification.
**Indicates how many rounds of the Delphi process were necessary to reach a consensus.

Weis, CMI 2015
SVM: supervised machine learning

Looking for a line separating points labeled differently

\[ f(x) = \sum_{i=1}^{n} w_i x_i + b \]

Cortes, Machine Learning (1995)
Coefficients for ESBL colonization after antibiotic therapy

Tacconelli, ECCMID 2016
1. Do not believe in anything simply because you have heard it.
2. Do not believe in anything simply because it is spoken by many.
3. Do not believe in anything simply because it is found written in your books.
4. Do not believe in anything merely on the authority of your teachers.
5. Do not believe in traditions... after observation and analysis, when you find that anything agrees with reason..., then accept it and live up to it.”
6. There are only two mistakes one can make along the road to truth; not going all the way, and not starting.
7. To be idle is a short road to death and to be diligent is a way of life.... wise people are diligent.
8. We are shaped by our thoughts; we become what we think. When the mind is pure, joy follows.
9. Concentrate the mind on the past and present moment.
10. An insincere and evil friend is more to be feared than a wild beast; a wild beast may wound your body, but an evil friend will wound your mind.
Conclusions

• Development of resistance should be considered as adverse event of antibiotic therapy.
• There is evidence that the impact of antibiotic therapy on the intestinal microbiota is depending from type of antibiotic, dosage, duration, and route of administration with long term effects that currently are still under investigation.
• Combination and sequential therapy impact differently according to patients' comorbidities and setting.
• Modulation of adverse effects through personalised antibiotic therapy could be addressed although feasible tool are still missing and impact on other outcome requires further analysis.