Rational antibiotic use in primary care

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University of Cape Town
Antibiotic resistance identified:

- penicillin-R Staphylococcus: 1940
- tetracycline-R Shigella: 1959
- methicillin-R Staphylococcus: 1960
- penicillin-R pneumococcus: 1962
- erythromycin-R Streptococcus: 1965
- gentamicin-R Enterococcus: 1967
- vancomycin: 1972
- gentamicin-R Enterococcus: 1979
- ceftazidime-R Enterobacteriaceae: 1985
- imipenem and ceftazidime: 1987
- vancomycin-R Enterococcus: 1988
- imipenem-R Enterobacteriaceae: 1996
- XDR tuberculosis: 1998
- linezolid-R Staphylococcus: 2000
- vancomycin-R Staphylococcus: 2001
- PDR-Acinetobacter and Pseudomonas: 2002
- ceftazidime-R Neisseria gonorrhoeae: 2003
- PDR-Enterobacteriaceae: 2004/5
- daptomycin: 2009
- ceftaroline: 2010
- ceftriaxone-R Neisseria gonorrhoeae: 2011

Antibiotic introduced:

- penicillin: 1943
- tetracycline: 1950
- erythromycin: 1953
- methicillin: 1960
- gentamicin: 1967
- vancomycin: 1972
- imipenem and ceftazidime: 1985
- linezolid: 2000
- daptomycin: 2003
*N gonorrhoea* resistance to 3rd generation cephalosporins
Global spread of KPCs

- **Canada 2008**: KPC-3 imported
- **USA 1996**: KPC-2 and KPC-3 endemic in some states
- **Colombia 2005**: KPC-2 and KPC-3 endemic
- **Brazil 2006**: KPC-2 endemic
- **Argentina 2006**: KPC-2 endemic
- **UK 2003**: Localised to northwest England
- **Ireland 2009**: KPC-2 sporadic
- **Portugal**: No clinical cases
- **France 2005**: KPC-2 sporadic
- **Finland and Sweden 2009**: Sporadic or imported
- **Poland 2008**: Five regional outbreaks
- **Hungary 2008**: Sporadic
- **Greece 2007**: KPC-2 endemic
- **China 2004**: KPC-2 and KPC-3 endemic
- **India 2002**: Sporadic cases reported
- **Israel 2005**: Endemic
- **Spain 2009**: KPC-2 sporadic
- **Italy 2008**: KPC-2 and KPC-3 endemic
- **Australia and New Zealand**: Imported
- **Global Spread**:
  - **KPC endemic and predominant**
  - **KPC scattered and predominant**
  - **KPC recorded, but not widespread**
  - **KPC recorded, but only from environmental sources**
  - **Other carbapenemase types scattered and predominant over KPC**
  - **Other carbapenemase types endemic and predominant over KPC**

Munoz-Price LID 2013
Emergence and spread of carbapenem-resistant *Enterobacteriaceae* in South Africa

Brink JCM 2012
Between 2000 and 2010:
Global consumption increased 36%
Most (76%) in BRICS countries
Increased consumption of carpapenems and polymixins
No positive impact on mortality

Life expectancy:
Belgium 79.2
Netherlands 79.4
Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least 2,049,442 illnesses,

23,000 deaths

*bacteria and fungus included in this report
Antibiotic use and resistance: population level

Goosens Lancet 2005
GAS erythromycin resistance correlates with use in Finland.
S *typhi* resistance correlates with use in Pakistan.
Antibiotic use and resistance: individual level

- *S. pneumoniae* resistance in OM after 3 - 4 days
  - 47% → 74% \((P = 0.004)\)
- New *S. pneumoniae* isolate in 16%
  - 84% were resistant to the drug the patient was receiving

Persistence of isolates with ↑ MICs after treatment
Rapid development of pharyngeal streptococcal macrolide resistance in healthy volunteers
Antimicrobial resistance in developing countries.
Part I: recent trends and current status

Iruka N Okeke, Ramanan Laxminarayan, Zulfiqar A Bhutta, Adriano G Duse, Philip Jenkins, Thomas F O’Brien, Ariel Pablos-Mendez, Keith P Klugman

“the general picture is one of accelerating rates of resistance spurred by antimicrobial misuse and shortfalls in infection control and public health”
Principles of outpatient antibiotic prescribing

1. Only use antibiotics for **bacterial infections**

2. Choose an **appropriate antibiotic**
   - Target the most likely pathogen for site of infection
   - Assess likelihood of resistance
   - Review contraindications
   - Choose drug with adequate target tissue penetration
   - Aim for single drug

3. Ensure **correct dose and route**

4. Correct **duration**
1. Does the patient need antibiotics?

Is there evidence of bacterial infection?
  • Fever
  • Leucocytosis with neutrophilia and left shift, toxic granulation
  • Raised inflammatory markers
  • Specific organ dysfunction (tachypnoea, dysuria, inflamed skin, etc)

- Yes
  - Needs empiric antibiotics

- Unstable
  - Withhold antibiotics
  - Investigate for potential focus of infection

- Unsure
  - Stable/well
  - Symptomatic treatment & look for other cause

- No
Risk versus benefit: Antimicrobial adverse drug reactions

- Minor ADRs common, include consequences of antimicrobial action such as diarrhoea & vaginal candidiasis
- Life-threatening ADRs:
  - Incidence generally $\leq 0.1\%$ e.g
  - Stevens-Johnson syndrome/TEN
  - Angioedema, anaphylaxis, bronchospasm
  - Hepatitis
  - Interstitial nephritis
  - Thrombocytopenia, neutropenia
Risk: benefit of treating common RTIs

- Rhinosinusitis: NNT = 7, NNT to harm = 190
- Common cold & purulent rhinitis: NNT = 15, NNT to harm = 12
- Otitis media: NNT = 24, NNT to harm = 78
- Acute bronchitis: NNT = 33, NNT to harm = 14

Numbers needed to treat vs. numbers needed to harm.
2. Choose an appropriate antibiotic

What is the most likely organism?
Assess the likelihood of resistance: community- or hospital-acquired?

• Hospital \( \geq 48 \) hours = high risk of antibiotic resistance:
  – Staphylococci resistant to cloxacillin
  – Gram negatives resistant to most \( \beta \)-lactams, gentamicin, quinolones

• Community resistance increasing:
  – *Streptococcus pneumoniae*
  – Gram negative bacilli
  – *Neisseria gonorrhoeae*
$\approx 40\%$ ESBL
(< 5\% CA ESBL)

Data courtesy Colleen Bamford
Table 32: Numbers and percentages of penicillin susceptible and non-susceptible isolates from invasive pneumococcal disease cases reported to GERMS-SA by province, South Africa, 2013. n=2,866.

<table>
<thead>
<tr>
<th>Province</th>
<th>Isolate not available</th>
<th>Susceptible*</th>
<th>Intermediate*</th>
<th>Resistant*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n   (%)</td>
<td>n   (%)</td>
<td>n   (%)</td>
</tr>
<tr>
<td>Western Cape</td>
<td>51</td>
<td>310  (73)</td>
<td>94  (22)</td>
<td>23  (5)</td>
</tr>
<tr>
<td>South Africa</td>
<td>933</td>
<td>1,397 (72)</td>
<td>456 (24)</td>
<td>80  (4)</td>
</tr>
</tbody>
</table>
Review contraindications

- Toxicity
- Allergy

Choose drug with adequate target tissue penetration

<table>
<thead>
<tr>
<th></th>
<th>CSF</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Coamoxiclav</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Poor (use if MRSA)</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Aim for a single drug with narrowest spectrum of activity
3. Correct dose and route of administration

• Inadequate dose: efficacy, selection of resistance
• Excessive dose: toxicity and cost
• Adjust for renal impairment
• Weight-based dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral absorption (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxil</td>
<td>85</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>90 (reduced by food)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>90</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>90</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>85 (do not give via NGT)</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>90</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0</td>
</tr>
</tbody>
</table>
4. Correct duration

- Longer courses increase risk of carriage of resistant strains
- Too short could lead to failure to eradicate
  - Especially at difficult sites (eg bone)
- Limited studies on duration
  - Prolonged therapy (≥4 weeks) difficult sites – endocarditis, bone.
  - In practice most treat for short (5 to 7 days) or intermediate (10 to 14 days).
Case 1

A 22-year-old man comes to your clinic complaining of a sore throat that started the previous day. A few of his colleagues have the same problem. On examination he is not acutely ill but has a fever of 37.8, generalised lymphadenopathy and an inflamed pharynx with no pus on the tonsils. His chest is clear.

1. What is the differential diagnosis?
2. How will you manage him?
Upper respiratory tract infection

DIAGNOSIS AND MANAGEMENT

Bacterial

- Acute onset
- Temperature >38°C
- Tender anterior cervical lymph nodes
- Age 3-15 years
- Previous rheumatic fever or rheumatic heart disease
- Pus or white patches on tonsils
- PCT > 0.25 ng/ml

Viral

- Rhinorrhoea
- Cough
- Diarrhoea
- Conjunctivitis
- Age >45 years
- PCT < 0.25 ng/ml

No antibiotics

Penicillin VK 500mg po 12hrly for 10 days or Benzathine penicillin 1.2 mU IM single dose
Antibiotics for sore throat

• Antibiotics used in 73% (only 5 - 17% caused by GAS)
  – Non-recommended antibiotics in 68%
  – Decrease in recommended Abx: 32 → 11%

<table>
<thead>
<tr>
<th>Table 3. Proportion of Adults With Sore Throat Given Any Antibiotic and Nonrecommended Antibiotics Over an 11-Year Period, by Primary Care Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antibiotic, %</td>
</tr>
<tr>
<td>Family practice</td>
</tr>
<tr>
<td>Internal medicine</td>
</tr>
<tr>
<td>General practice</td>
</tr>
<tr>
<td>Nonrecommended antibiotic for those receiving antibiotics, %</td>
</tr>
<tr>
<td>Family practice</td>
</tr>
<tr>
<td>Internal medicine</td>
</tr>
<tr>
<td>General practice</td>
</tr>
</tbody>
</table>

Linder JAMA 2001
Antibiotic prescription strategies for acute sore throat: a prospective observational cohort study

Paul Little, Beth Stuart, F D Richard Hobbs, Chris C Butler, Alastair D Hay, Brendan Delaney, John Campbell, Sue Broomfield, Paula Barratt, Kerenza Hood, Hazel Everitt, Mark Mullee, Ian Williamson, David Mant, Michael Moore, for the DESCARTE investigators

- Prospective cohort of 12000 patients with sore throat in primary care
- Complications in 1.4% (mild: OM, sinusitis)

<table>
<thead>
<tr>
<th></th>
<th>Immediate antibiotics</th>
<th>Delayed antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ complications</td>
<td>NNT 193</td>
<td>NNT 174</td>
</tr>
<tr>
<td>↓ reconsultation</td>
<td>NNT 40</td>
<td>NNT 18</td>
</tr>
</tbody>
</table>
Case 2

A 43 year woman, non smoker, previously well, presents with a 2 week history of productive cough. She reports subjective fever, and the symptoms have not resolved with cough syrup. Clinically she is afebrile, RR 16 with a clear chest.

1. How will you approach this?
2. Are antibiotics indicated?
Acute bronchitis

DIAGNOSIS AND MANAGEMENT

Acute cough (≤ 3 weeks’ duration)
PLUS
Normal vital signs and no signs of pneumonia chest examination
PLUS
Not associated with pneumonia on chest x-ray

Antibiotics not indicated
Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial

Paul Little, Beth Stuart, Michael Moore, Samuel Coenen, Christopher C Butler, Maciek Godycki-Cwirko, Artur Mierzecki, Slawomir Chlabicz, Antoni Torres, Jordi Almirall, Mel Davies, Tom Schaberg, Sigvard Mölsted, Francesco Blasi, An De Sutter, Janko Kersnik, Helena Hupkova, Pia Touboul, Kerenza Hood, Mark Mullee, Gilly O’Reilly, Curt Brugman, Herman Goossens, Theo Verheij, on behalf of the GRACE consortium

• 2000 patients included; randomised to amoxil 1g TDS for 7 days vs placebo
• No difference in primary outcome: duration of bad/worse symptoms

With amoxil:
• ↓ worse symptoms (16 vs 19%; NNT 30)
• ↑ adverse effects (29 vs 24%; NNH 21)
## Antibiotics for acute bronchitis (Review)

### Comparison 6. Clinically improved

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Number of patients reporting no activity limitations or described as cured/globally improved</td>
<td>11</td>
<td>3841</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.07 [0.99, 1.15]</td>
</tr>
</tbody>
</table>

### Comparison 12. Adverse effects

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Number of patients with adverse effects</td>
<td>12</td>
<td>3496</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.20 [1.05, 1.36]</td>
</tr>
<tr>
<td>1.1 Acute bronchitis studies</td>
<td>11</td>
<td>3162</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.22 [1.07, 1.40]</td>
</tr>
<tr>
<td>1.2 Subgroup with no placebo control</td>
<td>1</td>
<td>334</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.95 [0.61, 1.50]</td>
</tr>
</tbody>
</table>
Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database

- 3.36 million episodes of RTI
- Significant reduction in complications with antibiotics
  - But rare: NNT > 4000

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<table>
<thead>
<tr>
<th>Infection/adverse outcome (age group)</th>
<th>Adjusted odds ratio* (95% CI)</th>
<th>Number needed to treat (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>URTI/pneumonia (all ages)</td>
<td>0.68 (0.58 to 0.79)</td>
<td>4407 (2905 to 9126)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Otitis media/mastoiditis (all ages)</td>
<td>0.56 (0.37 to 0.86)</td>
<td>4064 (2393 to 13 456)</td>
<td>0.008</td>
</tr>
<tr>
<td>Sore throat/quinsy (all ages)</td>
<td>0.84 (0.73 to 0.97)</td>
<td>4300 (2522 to 14 586)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Chest infection/pneumonia (significant interaction between prescribing and age):
- 0-4 years: 0.22 (0.17 to 0.27), 101 (85 to 125), <0.001
- 5-15 years: 0.18 (0.13 to 0.24), 96 (73 to 137), <0.001
- 16-64 years: 0.27 (0.23 to 0.32), 119 (105 to 136), <0.001
- ≥65 years: 0.35 (0.33 to 0.38), 39 (36 to 42), <0.001

URTI=upper respiratory tract infection.
*Adjusted for age, sex, and social deprivation.

Petersen BMJ 2007
CRP for reducing antibiotic use in RTI

Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial

Paul Little, Beth Stuart, Nick Francis, Elaine Douglas, Sarah Tonkin-Crine, Sibyl Anthierens, Jochen W L Cals, Hasse Melbye, Miriam Santer, Michael Moore, Samuel Coenen, Chris Butler, Kerenza Hood, Mark Kelly, Maciek Godycki-Cwirko, Artur Mierzecki, Antoni Torres, Carl Llor, Melanie Davies, Mark Mullee, Gilly O’Reilly, Alike van der Velden, Adam W A Geraghty, Herman Goossens, Theo Verheij, Lucy Yardley, on behalf of the GRACE consortium

- Usual care vs CRP vs training in communication skills vs both
- 246 practices, > 4000 patients, LRTI > URTI

<table>
<thead>
<tr>
<th>No training</th>
<th>CRP</th>
<th>Communication</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>48%</td>
<td>33%</td>
<td>36%</td>
<td>Best results</td>
</tr>
<tr>
<td></td>
<td>RR 0.54 (0.42–0.69)</td>
<td>RR 0.69, 0.54–0.87</td>
<td>RR 0.38, 0.25–0.55</td>
</tr>
</tbody>
</table>

Lancet 2013; 382(9899):1175
PCT for for reducing antibiotic use in AECOPD

- RCT: 208 consecutive patients
- Significant reduction in Abx exposure (RR, 0.56; 95% CI, 0.43 to 0.73) and use (40% vs 72%)

No difference in mortality/recurrence at 6 months

Stoltz Chest 2007
PCT useful in all RTIs

Schuetz JAMA 2009
A 34-year-old HIV-infected man presents to you with a 5 day history of productive cough, fever, pleuritic chest pain and shortness of breath. On examination he is pyrexial, temperature 39.0°C, with a respiratory rate of 26 breaths per minute and bronchial breath sounds in the right middle zone. He is not confused and his blood pressure is normal. A chest X-ray confirms your suspicion of right middle lobe consolidation. Blood results show a urea of 10 mmol/L and white cell count of 20 x 10⁹/L.

1. What is the diagnosis? Commonest causes of this?
2. How will you manage this?
Does the patient have community acquired pneumonia (CAP)?

**Clinical evidence:** Fever and/or tachypnoea, and/or tachycardia, and/or breathlessness AND New or progressive infiltrate on chest X-ray

**Yes**

Severe CRB-65 ≥ 3

Admit to hospital

Severe CRB-65 ≥ 3

Ceftriaxone 1 g iv daily OR Co-amoxiclav 1.2g iv TDS for 5 days

PLUS Clarithromycin 500 mg po BD for 5 days

Consider empiric therapy for PCP if HIV-infected

**Not severe** CRB-65 ≤ 2

Outpatient treatment

Amoxicillin po 1g TDS for 5 days

Co-amoxiclav po 1 g BD for 5 days

Oral antibiotics ASAP

**No**

No antibiotics

Consider other causes (see guidelines for other RTIs)
A 24 year old woman presents with dysuria and frequency. There is no renal angle tenderness or fever. The dipstick nitrite and leucocyte esterase strips are positive.

1. What will you do?
2. What are the commonest causes of uncomplicated UTI?
3. What would you do if she had signs of pyelonephritis?
Cystitis

DIAGNOSIS AND MANAGEMENT

Symptoms
- Frequency, urgency, dysuria or suprapubic pain

PLUS
- Evidence of infection
  - Dipstick + for nitrite & leukocyte esterase
  - >1+ leukocytes on urine microscopy

Ciprofloxacin 500 mg po 12-hourly for 3 days
Pyelonephritis

**Symptoms**
Costovertebral angle pain and tenderness, often with fever

**DIAGNOSIS AND MANAGEMENT**

**PLUS**
Evidence of infection
Dipstick positive for nitrite and leucocyte esterase OR >1+ leukocytes on urine microscopy

Start empiric antibiotics

Severely ill or unable to tolerate oral

No

Outpatient

Ciprofloxacin 500 mg po 12-hourly

Yes

Inpatient

Ceftriaxone 1 g iv daily **OR** gentamycin 6 mg/kg/day iv

Switch to oral after clinical response & defervescence

De-escalate to narrower spectrum antibiotics
7 days for ciprofloxacin
14 days for cotrimoxazole or beta lactam