Hopes, Hypes and Multivallate Defences Against Antimicrobial Resistance
Professor Neil Woodford, Public Health England
Denver Russell Memorial Teleclass

Hopes, hypes and multivallate defences against antimicrobial resistance

Professor Neil Woodford (@Prof_Neil)
Antimicrobial Resistance & Healthcare Associated Infections (AMRHAI) Reference Unit

Hosted by Prof. Jean-Yves Maillard
Cardiff University, Wales

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Links between AMR …and Badbury Rings (Dorset) ?

- a multivallate iron age hillfort
- layers of challenging defence
- ..., but not impregnable!

http://www.castlesfortsbattles.co.uk
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The UK’s long record of high-level leadership

- AMR has a cyclical history
- hard now to be genuinely original
- much done, thought or written before
- recurring losses of momentum, necessitating new waves of activity

Jim O’Neill’s Review on AMR

Commissioned by the UK Prime Minister, July 2014 to revitalize antibiotic discovery — focused on economics.

"Drug-resistant infections already kill hundreds of thousands a year globally, and by 2050 that figure could be more than 10 million. The economic cost will also be significant, with the world economy being hit by up to $100 trillion by 2050 if we do not take action."

www.amr-review.org, 2015
Scientists kick back, 2016

“There is undoubtedly a large clinical and public health burden associated with AMR, but it is challenging to quantify the associated excess morbidity and mortality.”

“Current global estimates of the burden of AMR are not very informative; we need detailed, reliable data to be able to improve AMR control measures, preferably based on comprehensive, population-based surveillance data from low-, middle-, and high-income countries.”

“The AMR Review even acknowledged “that the reported numbers are “broad brush estimates,” [...] that “more detailed and robust work will no doubt be done by academic researchers,” and that there is a lack of data, urging for improvement of infection surveillance.”

Global commitment to combat AMR

- WHA 2014 resolution
- Global Health Security Agenda: AMR action package - mechanism and collaboration to accelerate implementation
- Many other national action plans
- UNGA, 2016
- UN Inter-Agency Coordination Group, 2017
Defining our defences against AMR

- Public awareness
- Sanitation and hygiene
- Antibiotics in agriculture and the environment
- Vaccines and alternatives
- Surveillance
- Rapid diagnostics
- Human capital
- Drugs
- Global Innovation Fund
- International coalition for action

Defence: New Drugs
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Countering the problem - then and now

We don’t have enough antibiotics in development to tackle the resistance issues we face now

…and the success of those in development is not guaranteed
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WHO Priority Pathogens list

- antibiotics specifically active against multidrug- and extensively drug-resistant Gram-negative bacteria.
- antibiotics for the paediatric population and for oral formulations for community diseases with a high morbidity burden such as drug-resistant *Neisseria gonorrhoeae*, *Salmonella typhi* and ESBL-producing *Enterobacteriaceae*.
- new classes of antibiotics without cross- and co-resistance to existing classes should be supported.
- must also reduce the burden of infections e.g. increased vaccination coverage, improved sanitation or sustained implementation of infection control measures.

New anti-Gram-negatives

<table>
<thead>
<tr>
<th>Name</th>
<th>Phase</th>
<th>Company</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone+ tazobactam</td>
<td>FDA approved Dec 19, 2014</td>
<td>Merck</td>
<td>Novel cephalosporin + beta-lactamase inhibitor</td>
</tr>
<tr>
<td>Ceftazidime+ avibactam</td>
<td>FDA approved Feb 25, 2015</td>
<td>Pfizer/Allergan</td>
<td>Cephalosporin + novel beta-lactamase inhibitor</td>
</tr>
<tr>
<td>Meropenem+ vaborbacam</td>
<td>FDA approved Aug 29 2017</td>
<td>The Medicines Company</td>
<td>Meropenem + novel beta-lactamase inhibitor</td>
</tr>
</tbody>
</table>

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### Most CPE are multi-resistant, 2016

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>E. coli</th>
<th>Klebsiella sp</th>
<th>Enterobacter/Citrobacter</th>
<th>C. freundii</th>
<th>MRSA</th>
<th>CRAB</th>
<th>VRE</th>
<th>E. faecalis</th>
<th>MRSE</th>
<th>CRAB</th>
<th>VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem (1 ÷ 2 mg/L)</td>
<td>96</td>
<td>96</td>
<td>96</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Meropenem (1 ÷ 2 mg/L)</td>
<td>42</td>
<td>96</td>
<td>96</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Moxifloxacin (0.5 ÷ 1 mg/L)</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Tetracycline (0.2 ÷ 0.5 mg/L)</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>80</td>
<td>100</td>
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<td>100</td>
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<tr>
<td>Gentamicin (1 ÷ 2 mg/L)</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

* = two isolates susceptible to antibiotic alone

---

### Developmental anti-Gram-negatives, May 2017

<table>
<thead>
<tr>
<th>Name</th>
<th>Phase</th>
<th>Company</th>
<th>Class</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPM + relebactam</td>
<td>Phase 3</td>
<td>Merck</td>
<td>Carbapenem + novel beta-lactamase inhibitor</td>
<td></td>
</tr>
<tr>
<td>Ceftarol (S649266)</td>
<td>Phase 3</td>
<td>Shionogi</td>
<td>Siderophore cephalosporin</td>
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</tr>
<tr>
<td>Omadacyclline</td>
<td>Phase 3</td>
<td>Paratek</td>
<td>Tetraacycline</td>
<td></td>
</tr>
<tr>
<td>Erapacycline</td>
<td>Phase 3</td>
<td>Tetraphase</td>
<td>Tetraacycline</td>
<td></td>
</tr>
<tr>
<td>Plezamycinid</td>
<td>Phase 3</td>
<td>Achaogen</td>
<td>Aminoglycoside</td>
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</table>
Assessing the potential of the antibiotic pipeline - I

Urgent threat pathogens

The Centers for Disease Control and Prevention considers three bacteria to be urgent threats to public health.1 While a number of promising antibiotics with the potential to treat infections caused by these bacteria are in the pipeline, more drug candidates are needed to meet current and future patient needs.

3 antibiotics are in development to treat drug-resistant gonorrhea infections. An estimated 246,000 drug-resistant cases occur in the United States each year.2

6 antibiotics are in development to treat patients with Clostridium difficile infections, which can sometimes result in life-threatening diarrhea. The CDC estimates that nearly 500,000 Americans acquired C. difficile infections in 2011; 15,000 of them died as a result.3

7 or more antibiotics are in development with the potential to treat infections caused by carbapenem-resistant Enterobacteriaceae (CRE). Infections caused by this resistant pathogen can kill up to 50 percent of patients if the bacteria infect the bloodstream.4

NOTE: This infographic is based on analysis as of March 2017.

Assessing the potential of the antibiotic pipeline - II

a) FDA fast-tracked molecules

b) ***Active vs. >90% UK CPE***

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Example: pan-aminoglycoside resistance (incl. plazomicin) in the UK

<table>
<thead>
<tr>
<th>RMTase</th>
<th>NDM*</th>
<th>OXA-48-like*</th>
<th>NDM + OXA-48-like</th>
<th>Other</th>
<th>Total</th>
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<tbody>
<tr>
<td>armA</td>
<td>140</td>
<td>22</td>
<td>17</td>
<td>3</td>
<td>182 (46%)</td>
</tr>
<tr>
<td>rmtB</td>
<td>43</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>55 (14%)</td>
</tr>
<tr>
<td>rmtC</td>
<td>51</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>63 (16%)</td>
</tr>
<tr>
<td>rmtD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>rmtF</td>
<td>28</td>
<td>47</td>
<td>3</td>
<td>0</td>
<td>78 (20%)</td>
</tr>
<tr>
<td>2 RMTases</td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>17 (4%)</td>
</tr>
<tr>
<td>Total</td>
<td>269 (57%)</td>
<td>79 (11%)</td>
<td>42 (82%)</td>
<td>6 (1%)</td>
<td>396 (21%)</td>
</tr>
</tbody>
</table>

c. 98% have NDM and / or OXA-48 like enzymes
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Assessing the potential of the antibiotic pipeline - III

A GO / NO GO decision: Delafloxacin Stumbles in Gonorrhoea Study

The treatment history of g. gonorrhoeae makes for fascinating reading. The organism has already been able to keep the upper hand in the war of drug versus drop. Once susceptible to sulfa drugs, to penicillin, tetracyclines and fluoroquinolones, it sequentially becomes resistant in the matter of a decade to every class of drug. At one time it looked like the organism would become PCU-susceptible again but the hope did not really materialize. Heres, we are at a bit of revulsion about the lack of knowledge about efficacy.

Now we hear that delafloxacin, a promising new fluoroquinolone, did not make the grade. According to a recent press release, Meridol’s delafloxacin had to skip the Phase 3 government study for reasons of "insufficient efficacy."

Cempra's solithromycin fails to match standard of care in GC study, development in NASH suspended; shares ease 10% premarket

Cempra’s (CMPR) SIVATION is down 10%, premarket as light volume, in response to its announcement that a Phase 3 clinical trial, SIVATION, assessing lead product candidate solithromycin compared to standard of care (rifampin/moxifloxacin plus oral azithromycin) for the treatment of uncomplicated gonococcal urethritis (GU) with or without perineal involvement failed to demonstrate the non-inferiority of solithromycin. The success rates for standard of care were 84.5% in microbiologically intent-to-treat population and 100% in microbiologically evaluable population compared to 80.5% and 81.1%, respectively, for solithromycin.

Too much publicity may be a bad thing

Anthony McDonnell and Neil Woodford: Hype can undermine hope for new antibiotics

January 22, 2018

Every time a newly discovered molecule or preclinical drug makes the headlines as a “cure for drug-resistant infections,” we ask people thinking that the problem has been solved.

Winning the “battle” against drug-resistant infections will require new antibiotics, as well as public and professional behavioral change, better diagnostics, hygiene practices, and vaccines—all to either reduce unnecessary antibiotic use or to limit the spread of infections. No single new antibiotic is going to completely solve the problem of resistant infections, nor are most of the antibiotics in the early stages of development likely to make it to market.

Yet researchers often tout early-stage successes in antibiotic development to the media as being potential game changers in preventing resistant infections. These statements are often misguided. Furthermore, they may undermine wider policy efforts to improve the research and development system for antibiotics because they create the impression that our current research system is adequate.
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Resistance to new agents: never say ‘never’!

“No, here, you see, it takes all the running you can do, to keep in the same place.”

Bacteria can be made resistant...

- In the lab:
  - In-vitro selection of CAZ-AVI mutants of *E. cloacae* and *K. pneumoniae*, all with the KPC-3 enzyme.
  - CAZ-AVI mutants at up to 16 x MIC, with frequencies of ca. $10^{-9}$
  - CAZ MICs rose; MICs of carbapenems, other cephalosporins and PTZ reduced
  - The most frequent change was Asp179Tyr, increasing CAZ specificity
  - Clinical relevance uncertain

- An ICAAC ‘top 10 beta-lactamase’ paper
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…or can become resistant in the clinic

- Clinical failure of CAZ-AVI in 10/37 CPE patients
- CAZ-AVI-R K. pneumoniae from three patients after CAZ-AVI for 10-19 d.
- D179Y/T243M, D179Y or V240G mutations in bla<sub>KPC-3</sub>, which were not present in baseline isolates
- MEM-S phenotype restored in K. pneumoniae from two patients; clinical successful R<sub>s</sub> in one case
- clinical impact of CAZ-AVI-R may be ameliorated if carbapenem-S is restored

New drugs, but the companies still pass the baton

The Medicines Company brings out the ax, looking to jettison hundreds of jobs in top-to-bottom restructuring

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Securing new drugs

- More predictable market to make antibiotics R&D commercially sustainable
  - lump-sum payments for ‘successful’ drugs
  - ‘de-link’ profitability from sales
- jump-start a new innovation cycle in antibiotics
  - Global AMR Innovation Fund
  - boost early-stage R&D into drugs and diagnostics
- reduce barriers to drug development
  - lower costs
  - improve the efficiency of research
  - lower global regulatory barriers

Need a more balanced reimbursement ‘ecology’

- overly committed to early-stage push funding
- limited late-stage push funding for clinical development
- almost no pull incentives to facilitate transition […] to commercialisation
New drug development vs. focus on antibiotic stewardship

- Not mutually exclusive
- In the future, new antibiotics must be viewed differently
  - not regarded as ‘cure more’ replacements by prescribers
  - not regarded as market blockbusters by manufacturers
- Changes in behaviour and expectation are essential

***This must be underpinned by better and faster diagnostics***
- old drugs should be used for ‘susceptible infections’
- new drugs must be held in reserve for ‘resistant infections’
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Why new AMR diagnostics?

• Prescribers must know earlier and more often that the infecting bacteria are susceptible to the drug they intend to use
  • Reduce empirical, broad-spectrum prescribing

• We need instruments and tests that can be deployed widely throughout the developed and developing world

• These new generations of diagnostics for AMR will facilitate
  • improved antibiotic stewardship
  • improved individual patient management
  • reduced onwards transmission of resistant bacteria

A recent UK analysis

“…many technologies are stuck at the laboratory phase or, having developed technical accuracy, have not progressed to clinical trials that provide cost-effectiveness and ultimately influence practice.”

Products are too often ‘pushed’ by industry, not “pulled” by clinicians

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Gonorrhoea: a paradigm for better AMR diagnostics

- International approach to treatment
- Recommendation changes when resistance rate exceeds 5%
- Many patients are over-treated to prevent under-treating a few
- Gonococci in UK (2016):
  - >85% are PEN-susceptible
  - >65% are CIP-susceptible
- Neither drug is used
- Can’t detect AMR at presentation

N. gonorrhoeae

- World’s first dual Rₐ failure:
  - Single case, no onwards transmission
  - MICs, CTR 0.25 mg/L; AZI 1 mg/L (both R by EUCAST)
- Outbreak of HL-AZI-R gonorrhoea
  - MICs, >256 mg/L (not a formal criterion)

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Defence: Better Surveillance

The complexities of AMR

- Antimicrobial Usage
  - All sectors
- Patients, non-human reservoirs
  - Hospital / community setting; risk factors; outcomes
- Host species
  - Strains, clones
- Genes etc.

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Monitoring antibiotic usage in England (ESPAUR)

- Established by PHE in 2013 in response to the strategy
- Focuses on bringing together NHS, PHE, Private sector across all prescribers and clinicians to improve
  - Surveillance data on antibiotic resistance and prescribing
  - Antimicrobial stewardship activities
  - Education and training for healthcare professionals
  - Education and awareness to public

Open access to surveillance data

- Fingertips: http://fingertips.phe.org.uk/
- AMR local indicators hosted on PHE fingertips site contain a selection of data across 5 domains:
  - Antimicrobial Resistance
  - Antibiotic Prescribing
  - Healthcare Associated Infection
  - Infection Prevention and Control
  - Antimicrobial Stewardship

- Indicators are intended as information for action and may enable healthcare organisations to benchmark the data for their organisation
Simple messages …for targeting action

WHO IS PRESCRIBING?

74%

General practice

11%

Hospital inpatients

7%

Hospital outpatients

5%

Dental professionals

3%

Other community settings

1 in 3 patients in hospitals & Emergency care settings use antibiotics in any given week.

1 in 3 individuals in England have at least one course of antibiotics each year.

...and more questions to challenge us

Age and sex standardised rates of E. coli bacteraemia, England 2015/16

- Regional variations in E. coli BSI rates
- Why?
- Socio-economic deprivation scores and other indices?
- Intervention measures
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We need to build global capacity

Available National Data* on Resistance for Nine Selected Bacteria/Antibacterial Drug Combinations, 2013

AMR surveillance in Africa

- no recent (>2013) AMR data published for >40% of countries on the continent and only a few of those were surveillance data.
- high level of resistance to commonly prescribed antibiotics in all regions:
  - trimethoprim (MR: 33.9%–100%), ampicillin (MR: 7.9%–100%) and penicillin (MR: 0%–75%)
- the standardization and quality of microbiological data must be improved.
  - unverified reports of highly unusual resistance patterns […], such as penicillin-resistant *S. pyogenes* and vancomycin-resistant *S. aureus*.
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Defence: Alert Reporting

"Everything more resistant than everything else"

National & international capacity building

- Without lab testing we’re blind to (the extent of) AMR problems
- Improve lab access; aim for a reference lab in every country / region
  - Each serving as the hub of a national network
  - Each acting as a spoke in an international network
- Performing essential techniques, proficient to international standards
- Sharing data / experience
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International AMR threats to healthcare

Colonized residents or visitors
Hospital treatment or travel overseas
Non-human reservoirs: foodstuffs (domestic or imported)
Inter-hospital transfers
Non-human reservoirs: animals and environment
Victims from conflict zones

- Multiple risks to be assessed to minimize damage
- Requires the detail to be understood

MDR & PDR Gram-negatives

- MDR increasingly seen in BSI across Europe
- PDR also a reality, but low numbers in most countries
- MBL + ESBL (all beta-lactams) + 16S RMTase (aminoglycosides)
- + resistance to colistin + upregulated efflux

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CPE in the UK, 2000-2017

Fighting ‘AMR’ outbreaks is hugely expensive

Superbug outbreak costs an NHS hospital one million pounds, says new study

Manchester trust struggling to contain hospital bug

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Discovery of plasmidic colistin resistance; mcr-1

If focus is on mcr we may lose sight of other colistin resistance

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Defence: Professional and Public Engagement

Communicating ‘AMR’ with graphics is not new

It was on a short-cut through the hospital kitchen that Albert was first approached by a member of the Antimicrobial Resistance.
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..., but is now mainstream and international

Groundbreaking UK engagement initiatives
AMR is a societal issue: many stakeholders

- Prescribers – primary and secondary / tertiary care
- Prescribers – veterinarians
- Other healthcare professionals
- Social scientists
- Agriculturalists
- Public Health – local, regional, national
- Patients / public
- Academia + educators
- Industry (pharma and diagnostics)
- Politicians
- Funding agencies
- International agencies and organisations

Summary

The fight against AMR needs action on multiple fronts:

- Advocacy at highest level, and engagement downwards
- Better education (prescriber, user and wider public)
- Reducing infections and onwards transmission
- Better diagnostics and wider adoption of them
- Laboratory capacity building
- Better surveillance data to inform (local, national and global) action
- Reducing inappropriate prescribing (multi-sectoral)
- Reducing duration of broad-spectrum antibiotic treatment
- Assessment of any unintended consequences
<table>
<thead>
<tr>
<th>Date</th>
<th>Title</th>
<th>Speaker</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 12, 2018</td>
<td>UNDERSTANDING RISK PERCEPTIONS AND RESPONSES OF THE PUBLIC, HEALTHCARE PROFESSIONALS, AND THE MEDIA: THE CASE FOR CLOSTRIDIUM DIFFICILE</td>
<td>Dr. Emma Burnett, University of Dundee, Scotland</td>
<td></td>
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<tr>
<td>April 18, 2018</td>
<td>GENETIC SIMILARITIES BETWEEN ORGANISMS ISOLATED FROM THE ICU</td>
<td>Prof. Slade Jenson, Western Sydney University, Australia</td>
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<tr>
<td>April 19, 2018</td>
<td>TOPICAL ANTIBIOTICS TO PREVENT POST-OPERATIVE SURGICAL INFECTION ... IS THE PARADIGM CHANGING?</td>
<td>Dr. Hilary Humphreys, The Royal College of Surgeons in Ireland</td>
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<tr>
<td>May 3, 2018</td>
<td>SPECIAL LECTURE FOR 5 MAY</td>
<td>Prof. Didier Pittet, University of Geneva Hospitals</td>
<td></td>
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<tr>
<td>May 10, 2018</td>
<td>HOW THE CERTIFICATION BOARD OF INFECTION CONTROL (CBIC) WORKS FOR YOU</td>
<td>To be announced</td>
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<td>May 17, 2018</td>
<td>THE SILENT TSUNAMI OF AZOLE-RESISTANCE IN THE OPPORTUNISTIC FUNGUS ASPERGILLUS FUMIGATUS</td>
<td>Prof. Paul E. Verweij, Radboud University Center of Expertise in</td>
<td></td>
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