5TH INTERNATIONAL DAY FOR FIGHTING INFECTION

ANTIBIOTIC DAYS:

WHICH FUTURE FOR ANTIBIOTICS?

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The Future

Study the past, if you would define the future.

Confucius

The future influences the present just as much as the past

Friedrich Nietzsche

The only thing we know about the future is that it will be different.

Peter F Drucker

Which futures?

- Pan resistance
- The broken market
- Squeezing the balloon
- ReAct

Pan Resistance: A Case History (Elizabeth Darley, NBT)

- Previous well UK subject
- Sustained extensive electrical burns in India
- Treated in two Indian hospitals with various antibiotics
- Returned to UK, directly to ICU with:-

  hypotension, acute renal failure, raised inflammatory markers requiring immediate resuscitation.

Pan Resistance: A Case History

Blood Cultures Day I

Vibrio spp

resistant to:- amoxicillin, co-amoxiclav, ceftazidime, ceftotaxime, ciprofloxacin, piperacillin-tazobactam, ertapenem, meropenem, gentamicin, amikacin, colistin.

Sensitive to: co-trimoxazole, tigecycline

Burn Cultures Day 1

Enterobacter cloacae	S only colistin
A.baumanii	S only colistin
A.lwoffi	S only tigecycline, colistin
Citrobacter freundii	S only colistin
E.coli	S co-trimoxazole, amikacin, colistin, tigecycline
P.aeruginosa	S only colistin
Kleb.pneumoniae	S only colistin

Pan Resistance: A Case History

Subsequent blood cultures:

Day 5	Acinetobacter baumannii	Colistin S only
Day 8	MRSA	
Days 8-9	P.aeruginosa	Colistin S only

Treated with:-

- 20 days teicoplanin
- 28 days colistin

Discharged home after 11 weeks

Pan Resistance: A Case History

Resistance Enzymes (Tim Walsh, University of Cardiff)

	Carbapenemases
Vibrio cholerae (non-01, non-0139)	NDM-1
Enterobacter cloacae[1]	NDM-1, AmpC
A.baumannii	OXA-23, OXA-51 like
A.lwoffi	OXA-23, OXA-51 like
Citrobacter freundii[2]	NDM-1
E.coli[3]	NDM-1
P.aeruginosa	VIM-2
K.pneumoniae[4]	NDM-1

Strains 1-4 carried blaNDM-1 on plasmids of 85K, 260K, 40K and 180K.

Strain 4 carried blaNDI-1 on IncN plasmid.

Pan Resistance: A Case History

- First case of polymicrobial NDM-1 positive infection
- First case of NDM-1 producing *Vibrio cholerae*

Illustrates several 'future' issues

- Population movement and resistance transfer
- The central significance of South Asia, China and Far East in generating resistance (Laxminarayan and Heymann BMJ 2012 344 e1567)
- Restricted choice of therapies, with existing rare Gram-negative isolates

The broken market

- Failure to develop new antimicrobials
- Failure to provide clinically relevant information for product users
- Failure of supply of generics

The broken market: New antibacterial drug approvals in the EU

2010-12:

- fidaxomicin
- ceftaroline (pending)

2000-2010

- doripenem
- ertapenem
- tigecycline
- daptomycin
- linezolid
- IV moxifloxacin
- retapamulin (topical)
- telithromycin

The broken market

Molecules in P1/2/3 development Q2/3 2011

Gram-positive agents optimised for MRSA therapies (old and novel targets)
Phase I - 5
Phase II - 9
Phase III - 5

Gram-negative agents
Existing targets/modes of action
Phase I - 1
Phase II - 3
Phase III - 3

Novel targets/modes of action
Phase I - 2

See. Ursula Theuretzbacher
IJAA 30(2012) 295-299

The broken market – The pipeline

More potent examples of existing classes

Aminoglycosides	Plazomicin (ACHN 490) – Ph2
Tetracyclines	TP2758 – Ph2
Cephalosporins	CXA101 – Ph2/3
Monobactams	BAL30072 - Ph1
(will be partnered with another B.lactam)	

B.Lactamase inhibitor combinations

Avibactam plus ceftaroline	Ph2/3
Avibactam plus ceftazidime	Ph3
CXA201 (tazobactam) plus CXA101 (ceftolozane)	Ph3
MK7655 plus imipenem	Ph1

New targets

POL7080	Ph1
Fatty acid synthesis inhibitors	?
Pleuromutilins	?
Boron containing small molecules GSK2251052 AN3365	Ph2

New delivery systems

BAY 41-6551 (amikacin)	Ph3

The broken market: Failure to supply relevant data for prescribers

Development Pathway - anti-Gram negative agents	Clinical need
Ph2 UTI cIAI	Enrich for resistant species P.aeruginosa, Acinetobacter, ESBL and other enzyme producers, QRDR mutations, elderly, pre-treated.
Ph3 UTI/acute PN	Enrich for resistance
Ph3 cIAI	Enrich for complexity, i.e. secondary drainage, deep abscesses, open abdomen, ICU, enrich for resistance
Ph3 HAP/VAP	HAP too ill defined VAP too rare Enrich for resistance

The broken market: Generics

Supply and cost issues – Europe

IV co-trimoxazole, IV fosfomycin, IV penicillin

Responsibilities of Generic houses for antibiotic resistance surveillance and updating SmPC's

The broken market: Future

- Too few new agents delivered to meet need in clinical practice (commercial, scientific, regulatory or medical reasons)
- Clinical trials continue to be uninformative for clinical use → large scale off - licence use
- Problems with supply and increasing cost of generics
- SmPC for marketed antibiotics are out-of-date and uninformative
- Evidence base for clinical guidelines erodes with changing clinical practice and increasing resistance

Squeezing the balloon:

Resistance trends in the British Isles since 2000

- S.pneumoniae — penicillin and macrolide resistance
- H.influenzae — B.lactamase production
- E.coli — cephalosporin, fluoroquinolone, aminoglycoside and carbapenem resistance
- S.aureus — oxacillin, macrolide, fluoroquinolone and vancomycin resistance

www.bsacsurv.org

Squeezing the balloon: Respiratory pathogens

Year	S.pneumoniae			H.influenzae
	Penicillin		Erythromycin	%B.lactamase producers
	%I	R	%R	
2001	8.8	0	14.1	20.8
2003	7.9	0.5	15.5	19.7
2005	4.3	0	13.0	16.1
2007	7.9	0	11.1	30.6
2009	4.3	0	9.0	25.4
2010	3.6	0	5.2	29.5

- Declining penicillin and macrolide resistance in S.pneumoniae ?reduced drug use in primary care ?vaccination
- Increasing B.lactamase production in H.influenzae

www.bsacsurv.org

Squeezing the balloon: MRSA & VRE: BSI

Year	S.aureus				Enterococcus
	OXA R MecA^{+}(%)	Erythromycin R(%)	Ciprofloxacin R(%)	$MIC_{50/90}$	Vancomycin %R
2001	43.3	41.2	37.3	1/1	7.7
2003	40.3	39.6	44.5	1/2	10.2
2005	35.7	31.1	33.2	1/2	16.5
2007	36.3	33.5	31.9	1/2	13.4
2009	22.8	24.5	22.7	1/2	14.4
2010	19.4	21.4	20.7	1/2	15.6

- Decline in MRSA; no evidence of vancomycin MIC creep (Reynolds et al, 2009)
- Increase in vancomycin resistant Enterococci

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Squeezing the balloon: E.coli BSI

	E.coli				
Year	CTX-R (%)	CTX-M producer %	Ciprofloxacin resistant %	Gentamicin resistant %	Imipenem resistant %
2001	-	0	8.2	4.1	0
2003	2.0	1.6	10.5	2.4	0
2005	7.7	6.1	16.6	6.5	0
2007	11.3	7.7	24.2	8.9	0
2009	6.8	5.4	13.6	4.1	0
2010	6.4	5.8	16.0	9.6	0

- Rise and fall of E.coli CTX-M producers ?due to MRSA intervention
- No detectable carbapenem resistance – first isolates in 2011

www.bsacsurv.org

Carbapenem Resistance in UK
(www.hpa.org.uk accessed 18th April, 2012)

	Number of Enterobacteriaceae from UK laboratories confirmed to have carbapenems						
Year	IMP	VIM	KPC	OXA-48	NDM	IMI	KPC+VIM
2003	1	1	1				
2004			3				
2005							
2006	3	1					
2007			1	1			
2008	1	2	5	9	5		
2009	9	4	13	15	32		
2010	9	26	229	29	44	2	
2011 (Q1 only)		19	31	5	7		1

Squeezing the balloon: BSI in England 2011

4 Centre Survey of BSI in Bristol, Leeds, UCL London and Newcastle
1131 patients recruited

Isolate	Incidence(%)
E.coli (non-ESBL)	29.9
Other Enterobacteriaceae	12.2
MSSA	9.5
S.pneumoniae	6.5
P.aeruginosa	5.3
E.coli (ESBL producer)	3.6 ←
Candida spp	3.4
MRSA	2.4 ←
Others	27.2

Squeezing the balloon future

- Isolated interventions reduce the incidence of some key pathogens: choice driven by public opinion, politics, professional pressure, public health and medical need.
- Reduced focus on “unimportant” or “new” mechanism of resistance, or pathogens, i.e. ESBL producer, carbapenemases, MSSA.
- Obvious opportunity for co-lateral benefit (?ESBL producers) or damage (MSSA BSI).
- Pragmatic and achievable in high income countries/regions.

ReActs Future: Action on Antibiotic Resistance

- Funded by Swedish International Development Agency

In USA – IDSA, in UK-BSAC, have similar visions

Themes:

- Promoting innovation
- Increasing visibility of antibiotic resistance
- Evidence generation
- Promotion of rational use

Innovating Novel Antibiotics
(So et al, BMJ 2012, 344 e1782)
(Editorial Paccaud BMJ 2012 344 e2591)

Resources
- Shared commercial compound libraries
- Building public sector compound libraries
- Shared access to medicinal chemistry
- Building public sector infrastructure
- Establishing public sector/private partnerships (infrastructure, specific disease areas, specific molecules)

Risks
- Direct public sector involvement by granting (Biomedical Advanced Research & Development Authority, BARDA; Wellcome Trust, EU Innovative Medicines Initiative (IMI) 2012)
- Involvement of disease specific patient driven charities

Rewards
- Market exclusivity (GAIN Act, fails to link use to rational use).
- ?Other

The Global Need for Effective Antibiotics: moving towards concerted Action 2010.

Reviving old antibiotics, prolonging use of existing antibiotics

- The diagnostics revolution, micro-lab automation, rapid diagnostics, MALDI-TOF.

- Improving the evidence base for present therapies (EU FP7 AIDA Programme: colistin, fosfomycin, tetracyclines).

- PK-PD dose optimisation
  (high dose, short duration, maybe combination, individualisation).

Conclusion

Which future then for antibiotics?

- Worldwide the future will be decided in South Asia and China (emergence of resistance, population, market size).
- Increased public sector investment in discovery in North America & Europe.
- Increase public sector funded evidence gathering for old agents (PD-PK, clinical trials, individualisation).
- Increase in commercially driven diagnostics (with cost driven centralisation of testing).
- No innovative anti-Gram negative drugs for at least 5 years: but incremental improvement.
- Efforts to improve regulation in EU and USA: ?ROW
- Focussed interventions on specific organism and resistances of concern in areas which can achieve this.

The best way to predict the future is to create it

Peter F Drucker