

**Inappropriate antibiotic usage in hospitals.  
How can we control it in developing countries?**



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[www.antibiyotik.org](http://www.antibiyotik.org)

**Common story**

- A Malaysian executive in his mid-thirties developed a stomach upset and diarrhoea after a meal. He consulted his company doctor. He left the clinic with six little white packets - two types of antibiotics, two types of painkillers (Ponstan and Panadol), a small white pill for diarrhoea, and a pink tablet to be chewed three times a day. He was flabbergasted. 'I thought I only needed something to control the diarrhoea until I got home.'

Third world network <http://www.twinside.org.sg/title/ong-cn.htm>

**Drug market 2002**



Class	World	Turkey
Cardiovascular	20	15
CNS	17	12
GIS	15	11
Respiratory	10	9
Antimicrobials	9	22
Locomotor	6	11
Urogenital	5	4

IMS Turkey, 2002

**Antimicrobial use in hospitals in Turkey**

- A multicenter point-prevalence study
- March 20, 2002
- 18 hospitals, 9471 patients
- Antimicrobial use 30.6%
- Treatment 44.8%
  - Empiric use 78.4%
  - Combination therapy ~33.0%
  - Inappropriate 25.8%
- Prophylaxis 44.2%
  - Inappropriate 33.7%

Usluer G, et al. Ann Clin Microb 2005;4(1):16

## Antibiotic use in Nigeria

- 96.7% of patients receiving at least one antimicrobial in hospital
- The number of antibiotics ~2.4/inpatient
- Only 4.2% of this antimicrobial prescribing was supported by susceptibility testing
- Polypharmacy is common in developing countries

Chukwuani CM, et al. Pharm World Sci 2002;24:188-95

## Surgical prophylaxis in Turkey

- A cross-sectional, country-wide survey
- 36 hospital, 439 physicians
- Use of 3rd g. cephalosporin 42%
- Duration < 24 hour 20%
- Duration >48 hour 46%
- Inappropriate time 39%
- Appropriate prophylaxis 26%

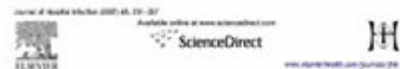
Hosoglu S, et al. Infect Control Hosp Epidemiol 2003;24(10):758-61

## Antimicrobial prophylaxis in cardiac surgery in Jordan

Appropriate use	%
Indication	100
Choice	1.7
Duration	39.4
Dose	27.9
Dosing interval	13.0
Timing	99.1

(97% have a previous midnight dose!)

Al-Momany NH, et al. J Manag Care Pharm 2009;15(3):262-71



### Device-associated hospital-acquired infection rates in Turkish intensive care units. Findings of the International Nosocomial Infection Control Consortium (INICC)

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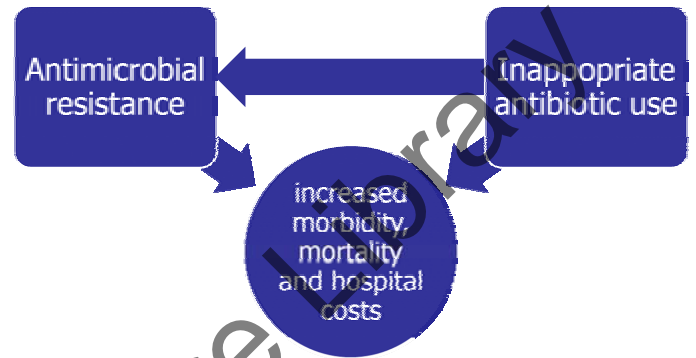
Micro-organisms	Antibiotic to which micro-organism is resistant	Percentage resistant
<i>Staphylococcus aureus</i> (MRSA)	Meticillin	89.2
Enterobacteriaceae	Ceftriaxone	48.2
Enterobacteriaceae	Ceftazidim	52.0
Enterobacteriaceae	Piperacilin-tazobactam	33.2
<i>Pseudomonas aeruginosa</i>	Ciprofloxacin	51.1
<i>P. aeruginosa</i>	Ceftazidim	50.7
<i>P. aeruginosa</i>	Imipenem	38.7
<i>P. aeruginosa</i>	Piperacilin-tazobactam	30.0
Enterococci	Vancomycin	1.9
<i>Acinetobacter</i>	Piperacilin-tazobactam	87.1

## Antimicrobial resistance & resource limitation level

- Extreme resource limitation
  - No antibiotic, no resistance
- Extreme to moderate resource limitation
  - Inconsistent antibiotic use, suboptimal dosing, use of counterfeit drugs, some excessive use, excessive resistance
- Moderate to minimal resource limitation
  - Inappropriate use, excessive use, using broad spectrum antibiotics, excessive resistance

DiazGranados CA, et al. Int J Antimicrob Agents 2008;32:1-9

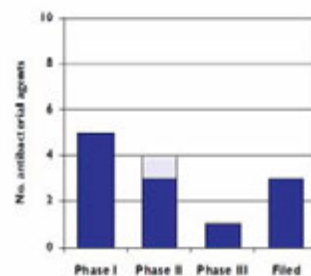
## Global problem



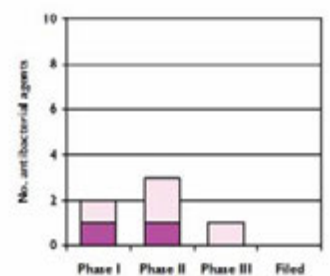
## Solution

- Antimicrobial stewardship
  - Rational use of available antibiotics
- Investment in new antimicrobial drugs
- Hospital infection control

## New antimicrobials



Gram-positive bacteria: 13 antibiotics



Gram-negative bacteria: 6 antibiotics

Dellit TH, et al. Clinical Infectious Diseases 2007; 44:159-77

Source eCDC, EMEA, 2009.  
[http://ecdc.europa.eu/en/publications/Publications/0909\\_TER\\_The\\_Bacterial\\_Challenge\\_Time\\_to\\_React.pdf](http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf)

## Classical strategies (Antimicrobial stewardship programs)

- Provide an antibiotic formulary
- Provide an antibiotic order form
- Restricted use of antibiotics
  - Prior authorization of prescriptions by ID
- Provide automatic stop orders
- Install an infection prevention committee
- Provide written antibiotic guidelines
- Provide an antibiotic booklet

Hulscher MEJL, et al. Lancet Infect Dis 2010;10:167-75

## Developing countries

- Developing countries are highly diverse group
- Have different health care systems
- Patterns of antibiotic dispensing are different
- Insurance coverage is different
- Have different problems
  - Starvation
  - Limited access to clean water

## Developing countries

- Lack of local and national policies
- Lack of trained personnel
  - ID, clinical microbiologist, epidemiologist
- Lack of diagnostic facilities
- Limited antibiotic supply
- Poor quality of antimicrobials
- Misconceptions about antimicrobials
- Poor medical records
- Inadequate epidemiologic information
- Inadequate staffing, overcrowding in hospitals
- Lack of infection control practices

Okeke IN, et al. Emerg Infect Dis 1999;5:18-27  
Sirinavin S & Dowell SF. Semin Pediatr Infect Dis 2004;15(2):94-8



Intensive care unit in Uganda



Over-the-counter drug



Counterfeit drug

Fisher-Hoch SP. British Medical Bulletin 2005;73 :123-137  
Hart CA, Kariuki S. BMJ 1998;317:647-50, Newton PN, et al. PloS Med 2006;3:e197  
Rosenthal VD. Lancet 2010;377:186-8

## Factors driving antibiotic use/choice

- Reimbursement policy
- Episode-based payment
- Limited or unstable antibiotic supply
- Pressure of pharmaceutical promotion



## Obstacles: Personal

### Knowledge

- Lack of knowledge of magnitude of antibiotic resistance
- Specific beliefs on antibiotics
- The new and expensive drug is better
- Antibiotics are risk free
- Diagnostic uncertainty; viral v.s. bacterial
- Undistinguishing infection, colonization, and contamination

### Attitude

- Previous experiences
- Prescribing antibiotics for all patients with fever
- Poor modeling

Hulscher MEJL, et al. Lancet Infect Dis 2010;10:167-75  
 Hluscher MEJL, et al. Int J Med Microbiol 2010;300:351-6  
 Radyowijati A & Haak H. Social Science & Medicine 2003;57:733-44

## Obstacles: External

- Organisational
- Social
- Political
- Economical

Lack of laboratory equipment  
 Delay in delivering of laboratory results  
 Antibiotics are not present in the ward  
 Lack of time

Senior doctor knows everything, no criticism  
 Pressure of patients for antibiotic prescription

Poverty  
 Income inequality  
 Low budget for healthcare

Hulscher MEJL, et al. Lancet Infect Dis 2010;10:167-75  
 Hluscher MEJL, et al. Int J Med Microbiol 2010;300:351-6

## Antibiotic decision

- Made by gatekeepers (residents)
  - Give the best antibiotic to prevent disaster!
    - Safe sleeping!
  - Ordering antibiotic combinations
    - Usually unneeded

Hulscher MEJL, et al. Lancet Infect Dis 2010;10:167-75

## Suboptimal decisions

- Using antibiotic without indication
- Using longer duration of antibiotics
- Using broad-spectrum antibiotics
- Inappropriate dose (low or high dose)
- Unnecessary combinations

## What can we do?



## Controlling antibiotic use

- A strong national policy
- Commitment to a national antimicrobial resistance task force with a budget
- Introduction of infection control programs
- Adequate institutional or governmental support for IDs
- Quality assurance for antimicrobials
- Restriction of over-the-counter dispensing of antimicrobials without prescription
- Improvement in laboratory diagnosis

## Who should be aware about antibiotic resistance?

- National level
  - Policy makers
  - Opinion leaders
  - Politicians
  - Press media
- Local level
  - Hospital administrators
  - Chief of departments/wards

## Improving teamwork


- Be part of decision
- Internalize the principles of antibiotic prescribing
- Introduce multidisciplinary ward rounds
- Encourage ID consultation
- Participate ID journal club
- Provide feedback
- Provide reminders
- Collaboration with laboratory

Charani E, et al. JAC 2010; 65: 2275–2277  
Hulscher MEJL, et al. Lancet Infect Dis 2010;10:167-75

## Process and outcome measurements

- Before-after studies
- Surveillance antimicrobial resistance
- Prospective collection of antibiotic consumption data
  - Defined daily dose
- Cost of treatment

## Changing professional behaviour



Education

Feedback

Motivation

Awarding

Financial incentives

Hulscher MEJL, et al. Lancet Infect Dis 2010;10:167-75

## Education: Changing habits & knowledge

- Integrating antimicrobial therapy modules into standard curricula
- Physicians, nurses, pharmacists and other health care professions
- Problem-based learning
- Continuing education programs by societies
- Focus group discussions
- Meetings
- Seminars
- Workshops



Okeke IN, et al. Lancet Infect Dis 2005;5:568-80  
Thomson O'Brien MA, et al. Cochrane Database Syst Rev 2001;(2):CD003030

## Collaboration with media

- Training media editors, journalists
  - Responsible health reporting
- Media campaigns
- TV series, spots
- Radio programs
- Social media



## Tippy tap

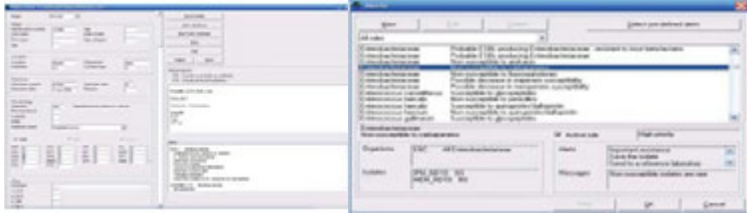


## Simple solutions

- Lack of information technology
  - Written antibiotic order forms
- There is no physician trained in infectious diseases
  - Internal medicine, clinical microbiologist could lead the program
- Microbiology laboratory
  - Able perform resistance testing at least for key pathogens (e.g. Disk diffusion)
    - E. coli, Acinetobacter spp. S. aureus



## WHONET software



- Analysis of laboratory findings
- Antimicrobial susceptibility test statistics
- Outbreak detection
- Integrated susceptibility test interpretation
- Clinical alert
- Microbiological alert



## Free data management



## Networks

- Alliance for the prudent use of Antibiotics (APUA)
- European Antimicrobial Resistance Surveillance network (EARS-NET)
- Asian Network for Surveillance of Resistant Pathogens (ANSORP)
- Pakistan Antimicrobial Resistance Network (PARN)
- Global Antibiotic Resistance Partnership (GARP)
- Pan American Health Organization (PAHO)



## Single strategy: prioritising

- Surgical prophylaxis
- De-escalation therapy
- Avoiding combination therapy
- Avoiding vancomycin for single CoNS blood culture
- Reduction of *C. difficile* infection
- Restricted use of some antibiotics
  - Clindamycin
  - Rifampicin
  - Ceftazidime
  - Carbapenems

## Antibiotic control regulation in Turkey

## Antibiotic control regulation in Turkey February 1, 2003

- Antibiotic control regulation (2003)
  - Reimbursement policy
  - National meeting with IDs from ID departments
  - Standard teaching slides
  - Local meetings (2003-2004)
- Infection control regulation on inpatient healthcare facilities (2005)
  - Establishment of HICC is compulsory in > 200-bed hospitals
- Certification program for IDs and infection control nurses (2006)

Policy		Antibiotics
Unrestricted agents		Penicillins, amox/clav, oral cephalosporins, macrolides, ciprofloxacin, gentamicin, clindamycin, tetracycline, cotrimoxazole, metronidazole
Partly restricted	Specialist	Rifampisin, streptomycin, antivirals, new generation quinolones
Controlled agents (A-72)	Specialist	3-4 g. Cephalosporins, amikacin, netilmicin, parenteral quinolones
Restricted agents	Infectious diseases	Pip/tazo, carbapenems, glycopeptides, linezolid, tigecycline, daptomycin, liposomal, amphotericin B, voriconazole, anidulafungin, caspofungin, itraconazole

## Impact of restriction policy on antibiotic consumption

The image shows three examples of antibiotic prescription forms. Each form has columns for 'Antibiyotikler' (Antibiotics), 'Doz ve Doz Aralığı' (Dose and Dose Interval), 'Uygulama' (Application), and 'Süre (gün)' (Duration). The forms are handwritten and show various antibiotic prescriptions.

	Before*	After*	Difference %	Cost reduction %
Ozkurt Z.	37.34	32.02	14.2	18.5
Arda B.	5.12	3.78	26.0	26.0
Hosoglu S. **	71.56	52.64	26.4	

\*DDD/100 patients-day

\*\*Multi-center study

Arda B, et al. J Infect 2007;55(1),41-8  
Hosoglu S, et al. Eur J Clin Pharmacol 2005;61(10):727-31  
Ozkurt Z, et al. Jpn J Infect Dis 2005;58(6),338-43

## Impact of restriction policy on appropriate use of antibiotics

	Before %	After %
Appropriate use	55.5	66.4
restricted		88.4
unrestricted		58.2

## Results of studies in Turkey

- Restricted antibiotic used is decreased ☺
- Unrestricted antibiotic use is increased ☹
- Appropriate use of restricted antibiotics is increased ☺
- The cost of antibiotics is decreased ☺

Ozkurt Z, et al. Jpn J Infect Dis 2005;58(6),338-43

Arda B, et al. J Infect 2007;55(1),41-8  
Hosoglu S, et al. Eur J Clin Pharmacol 2005;61(10):727-31  
Ozkurt Z, et al. Jpn J Infect Dis 2005;58(6),338-43  
Tunger O, et al. J Infect Developing Countries 2009;3(2):88-93

## Conclusion

- Adequate governmental and institutional support
- Adequate budget
- Education for changing knowledge and behavior
- Strengthen the laboratory and epidemiological capacity
- Introduction of infection control programs
- Team working

