Principles of Antibiotic Stewardship

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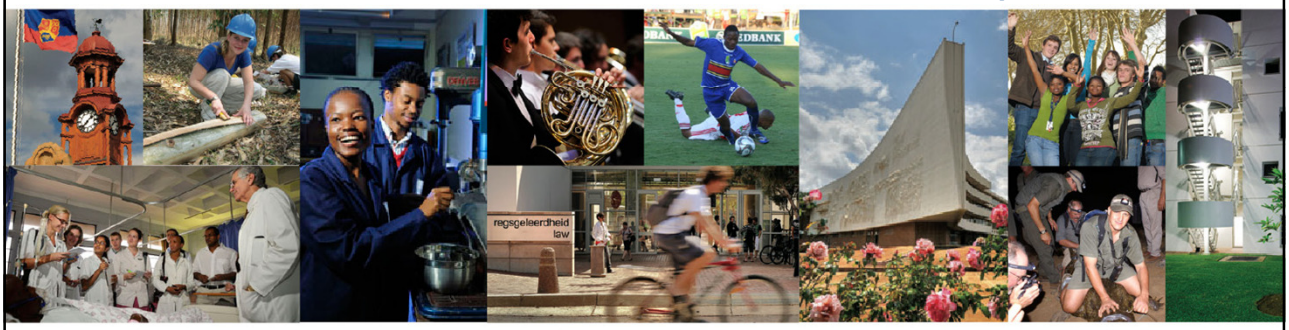
Paediatric Infectious Diseases
10 September 2014



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SAPA 2014
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Good antimicrobial stewardship is a practice to ensure …

- optimal selection, dose, and duration of an antimicrobial therapy …
- best clinical outcome …
- producing the fewest toxic effects …
- the lowest risk for subsequent resistance…

"Antibiotic stewardship refers to a multifaceted approach … to optimise prescribing, including policies, guidelines, surveillance, education and audit."

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Mendelson, SAMJ 2012

What does it mean…

Afrikaans: "*Antibiotika rentmeesterskap*"

- Rentmeester = *oikonómos* (Greek)
  - manager of household or of household affairs

Zulu: "*nobuphathi antibiotic*"

- Other nouns
  - *Umphathi* = manager, holder, conductor / "the boss"
  - *Inceku* = household servant


including
Responsible
Board
draft
Health
people
ensure
Parliamentary
providing
Business
HMRC
delivery
staff
strategy
development
customer
UK
Department
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aspects
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operational
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Defence
issues
provide
across
Director
advice
Government
effective
capability
Service
planning
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legal
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Programme
Management
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within
provides
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Head
Directorate
customers
specialist
Secretary
Development
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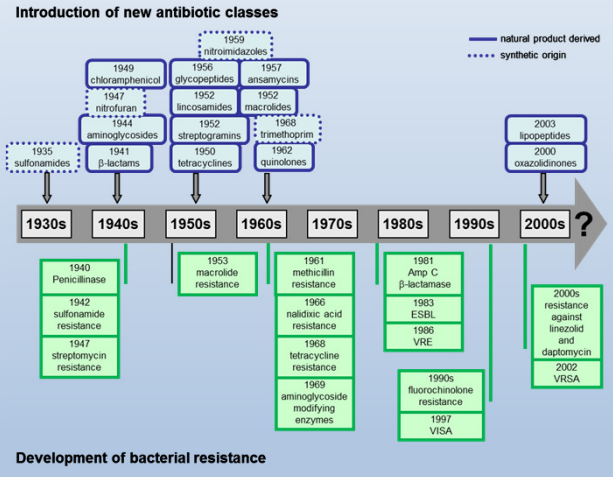
Tax
responsibility
commercial
training
assurance
managing
government
information
Customer
new
National
Chief
senior
required
expertise

Where did it start?

"An epic struggle for survival between single-celled bacteria and developing mammalian species has existed from time immemorial."



"Pan-drug–resistant"

"Extremely drug-resistant" pathogens

Robert C. Owens Jr, Diagnostic Microbiology and Infectious Disease 2008

Where did it start?

- "He (the prescriber) is under great pressure to prescribe the 'newest', 'best', 'broadest' antibiotic preparation, prescribe it for any complaint whatever, quickly, and preferably without worrying too much about specific etiologic diagnosis or proper indication of the drug"

  (Jawetz, 1956)

- 1970s and 1980s: a formal program at Hartford Hospital formed the1e ASP
- RCT in the late 1990s: antimicrobial use could be significantly reduced without adversely impacting clinical outcome
- In 2007: Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) jointly published guidelines for the development of ASP

IDSA Infectious Diseases Society of America

SHEA The Society for Healthcare Epidemiology of America

South Africa…

Wake up, South Africa! The antibiotic 'horse' has bolted…

Emergence:

- New Delhi metallo-β-lactamase-1 (NDM-1)
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Klebsiella pneumoniae carbapenemases (KPCs)

"…we must force a return to rational antibiotic prescribing, with equal emphasis on addressing IPC..."

"*not the domain of the few, but the responsibility of all*"

Mendelson SAMJ 2012

South Africa…

Unlike the case of drug-resistant tuberculosis or HIV…

MDR Gram-negative bacteria (ie. CRE) cannot be blamed on poor patient compliance, or resistant strains from foreign climes.

This is a home-grown problem, generated and perpetuated by doctors, nurses and allied healthcare workers in South Africa.

SAASP
SOUTH AFRICAN ANTIBIOTIC STEWARDSHIP PROGRAMME

Best care Always!

Mendelson SAMJ 2012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federation of infectious diseases societies of southern africa
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Wake Up South Africa the 'Antibiotic Horse' Has Bolted [SAMJ 2012]
Prevalence of Infection in South African Intensive Care Units (PISA) Study [SAMJ 2012]
Groote Schuur Hospital AMS Programme [PLoS One 2013]
Colistin Resistant OXA-181-Producing Klebsiella Pneumoniae in South Africa [Jrnl Clin Microbiol 2013]
Hand hygiene Patient Empowerment [SAJEI 2014]
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Antibiotic stewardship programmes (ASP)

- Two main types:
  - Restrictive (formulary restriction and pre-authorisation)
  - Educational (audit and feedback)

Table 1. Core elements of antimicrobial stewardship programmes

Tactic	Level of evidence [a]	Comment
Guidelines and clinical pathways	A-I	Core activity, but implementation plans are critical
Education	A-III	Critical, but must be ongoing and interactive
Antimicrobial cycling/mixing/diversity	C-II	Might work if done very frequently Diversity probably best
Antimicrobial order forms	B-II	Focuses decision making Shortens duration of treatment
PK/PD dose optimisation	A-II	Improves outcome Prevents resistance
Combination therapy	C-II	Increases antibiotic exposure Mainly theoretical benefit Likely to be most beneficial at start of treatment
Streamlining or de-escalation	A-II	Reduces use of broad-spectrum agents
Intravenous to oral switch	A-III	Reduces costs and length of intravenous access May not help with resistance per se

[a] Strength of recommendation: A, good evidence to support a recommendation for use; B, moderate evidence to support a recommendation for use; C, poor evidence to support a recommendation for use.
Quality of evidence: I, evidence from ⩾1 properly randomised, controlled trial; II, evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled experiments; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

International Journal of Antimicrobial Agents 34, S3 (2009) S2 S5

Antibiotic stewardship programmes (ASP) in paeds

- Strategies:
  - Core (restriction and/or audit and feedback)
  - Supplemental

TABLE 1. Antimicrobial Stewardship Strategies

Antimicrobial Stewardship Strategy	Description	References
Core Strategies		
Prospective-audit with feedback	Review and provide feedback on antibiotics after they have been ordered	3
Prior approval	Review and approve antibiotic prior to initiation	4
Supplemental Strategies		
Education	Lectures, educational conferences, handbooks	12
Clinical guidelines	Guidelines can incorporate appropriate antibiotic selections and dosing	13
Streamlining/de-escalation therapy	Focus on identifying bug-drug mismatches* and stopping antibiotics when cultures are negative	4,8
IV to PO conversion	Changing antibiotics with good bioavailability to oral (eg, linezolid, clindamycin, fluoroquinolones)	14
Dose optimization	Assuring the appropriate doses are being administered for the given clinical condition	4,8
Antimicrobial order forms	Require clinicians to justify antibiotic use and can provide automatic stop orders within the form	15

*Bug-drug mismatch—When the spectrum of the antibiotic being used to treat the organism is either too broad (eg, vancomycin to treat methicillin susceptible *Staphylococcus aureus*) or too narrow (eg, the organism is resistant).

Pediatr Infect Dis J 2010;29: 862–863

Antimicrobial Stewardship in Pediatrics How Every Pediatrician Can Be a Steward

- Goals of AS:
  - to optimize outcomes while minimizing consequences (toxicity, the selection of pathogenic organisms, and the emergence of resistance)
- 2010:
  - Pediatric Infectious Diseases Society (PIDS) formed the Pediatric Committee on Antimicrobial Stewardship:
    - advance pediatric AS
    - promote research in pediatric AS
    - develop AS educational programs
    - sponsor and organize an annual conference on pediatric AS

Pediatric Infectious Diseases Society

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JAMA Pediatr. 2013;167(9):859-866.

Table 1. Principles and Strategies for AS Programs

Principles	Examples of Strategies
Timely antibiotic therapy management	Ensuring prompt initiation of antibiotic therapy when indicated Critical illness such as sepsis High-risk patients with serious bacterial infections Avoiding use of antibiotics when not indicated Viral upper or lower respiratory tract infections Asthma exacerbations Viral pharyngitis Use of clinical guidelines and algorithms that facilitate provider recognition of clinical syndromes that do and do not require antibiotics
Appropriate selection of antibiotics	Ensuring that proper antibiotic regimens are selected for specific clinical syndromes and infections Minimizing redundant antibiotic regimens for gram-negative or anaerobic bacterial infections Use of antibiograms and clinical guidelines to optimize antibiotic selections
Appropriate administration and de-escalation of antibiotic therapy	Ensuring proper dosing of antibiotics Peer review of antibiotic use at 48-72 h after initiation to determine if therapy should be continued, changed, or discontinued Monitoring for serum therapeutic levels of antibiotics Proper administration of antibiotics for surgical prophylaxis
Use of expertise and resources at point of care	Formation of multidisciplinary AS committees Obtaining administrative and leadership support
Continuous and transparent monitoring of antibiotic use	Auditing antibiotic use to identify opportunities for stewardship and education Prospective monitoring to assess efficacy of AS program

Abbreviation: AS, antimicrobial stewardship.

JAMA Pediatr. 2013

1. Appropriate and Prompt Antimicrobial Therapy Initiation

- *"All or nothing…"*
  - Risk factors for serious bacterial infections (CVP/HIV) = prompt and appropriate antimicrobial therapy when an infection is suspected
  - Protocols and interventions to reduce time to antibiotic administration (prompt physician order and AB access in emergency carts)
  - Prevent overuse of antibiotics in clinical situations where antibiotics are not indicated (asthma, pharyngitis, and RSV bronchiolitis)
- *Education and feedback to prescribers*

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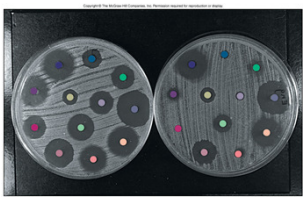
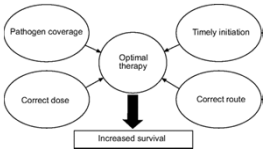
2. Appropriate Selection of Antibiotics

- *"All or something…"*
- Appropriate empirical antimicrobial regimen
- Prerequisite:
  - Local antibiograms
  - Clinically relevant antibiograms



"Escherichia coli first episode of urinary tract infection vs strain from 3rd episode and VU reflux"

  - Appropriate testing / sampling*



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*Paediatrics & child health 2014

3. Appropriate Administration and De-escalation

- *"Double-check the script…"*
- Correct dosing: prospective surveillance and therapeutic level monitoring (vancomycin, aminoglycosides, voriconazole)

- "*Time for a change…*"
- Appropriate and timely de-escalation or discontinuation (best recognized and most widely adopted principle of AS)
  - Reducing the number of antibiotics
  - Selecting narrow- over broad-spectrum antibiotics
  - Converting parenteral to oral therapy

Let's Go PO -
Transitional Antimicrobial Therapy

Benefits of Oral Therapy

- Equally effective as IV
- Shortened Length Of Stay
- Fewer bacteremias
- Reduction in administration and preparation time
- Decreased drug cost

Which Antimicrobial Agents?

Agents with ≥90% bioavailability:

- Ciprofloxacin
- Gatifloxacin
- Fluconazole
- Metronidazole
- Clindamycin
- TMP/SMX
- Doxycycline
- Minocycline
- Cephalexin
- Rifampin
- Linezolid

Agents not absorbed well or at all from the GI tract:

- Vancomycin
- Neomycin
- Paromomycin
- Nitrofurantion (good for UTIs only)

When to Transition?

- Functional GI tract
- Stable vital signs
- WBC normalizing

Which Infections?

Infections amenable to transitional therapy:

- Respiratory tract infections
- Urinary tract infections including pyelonephritis
- Skin and soft tissue infections
- Intra-abdominal infections

Avoid:

- Meningitis
- Acute osteomyelitis
- Endocarditis
- Staphylococcal bacteremia of unknown origin
- Undrained abscesses
- Septic shock
- Persistent fever and neutropenia
- Mucositis

How to Transition

Transitioning from the same drug to the same drug is straightforward:

- e.g., gatifloxacin IV to gatifloxacin PO (exception: Clindamycin 600 mg IV → 300 mg PO)

Other options:

- Piperacillin/tazobactam
  - Ciprofloxacin* + clindamycin
  - Ciprofloxacin* + amoxicillin/clavulanate
  - Gatifloxacin* + metronidazole
- Cefepime
  - Ciprofloxacin* + cephalexin
  - Gatifloxacin* (use ciprofloxacin if documented P. aeruginosa)
- Imipenem
  - Ciprofloxacin* + amoxicillin/clavulanate
  - Gatifloxacin* + amoxicillin/clavulanate (use ciprofloxacin if documented P. aeruginosa)
- Oxacillin or Cefazolin
  - Cephalexin
  - Gatifloxacin*
  - Minocycline

Check culture and susceptibility results.

*When fluoroquinolones are transitioned from IV to PO, remember to space interacting medications such as sucralfate, Mg^{++}, Fe^{++}, Zn^{++}, Ca^{++}, and Al^{+++} by two hours (before or after).

4. Use of Expertise and Resources at POC

- Local AS teams or committees composed of experts from multiple fields…
- In addition, support from hospital administration…

- Newland (2010): "*It is not possible to have an ASP without the support of the hospital administration*."

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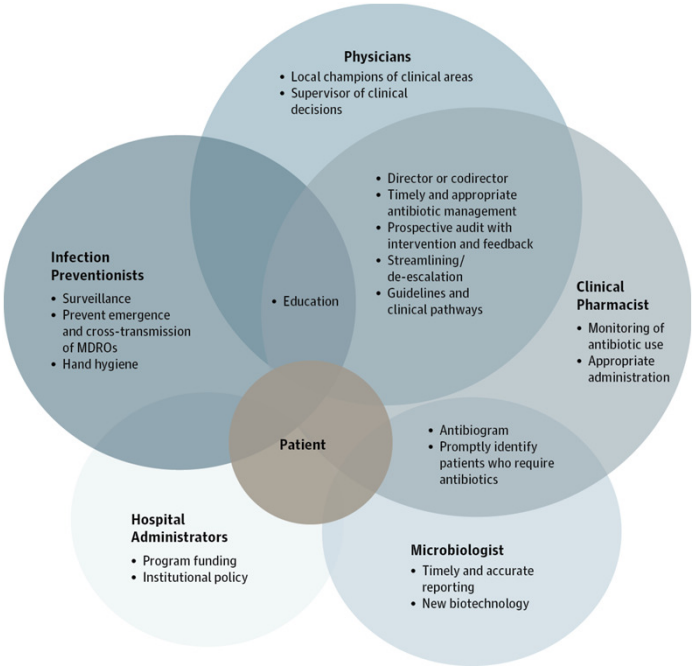
Pediatr Infect Dis J 2010;29: 862–863

Use of Expertise and Resources at POC



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5. Continuous and Transparent Monitoring

- Surveillance…
- *Remember the context…*
- *"M&M AB-pathogen profile"*

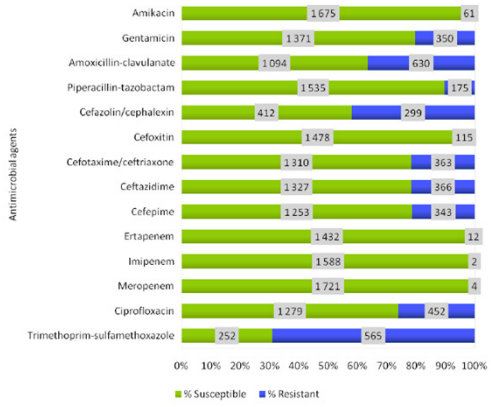

Figure 4: *Escherichia coli* cases by month, and numbers and percentages of susceptible and resistant *E. coli* isolates from blood cultures at public-sector sentinel sites, 2013. Total number of isolates analyzed = 1773.

ANTIMICROBIAL RESISTANCE SURVEILLANCE FROM SENTINEL PUBLIC HOSPITALS, SOUTH AFRICA, 2013

Olga Perovic, Melony Fortuin-de Smidt, Verushka Chetty

Centre for Opportunistic, Tropical & Hospital Infections, NICD

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Monitoring Outcomes

ASP process measurement outcomes

- Antibiotics doses / 1000 pt days
- Cost benefits
- Prescription errors
- Safe and appropriate transitions

Patient oriented clinical outcomes

- Lengths of hospital or ICU stays
- HAIs
- Readmissions
- Mortality
- *Clostridium difficile* infections
- Adverse drug-associated events

Outcome examples…

- "Impact on reducing targeted- and non targeted-antimicrobial use"

Pediatrics 2011 Dec;128(6):1062-70

- "Reduction vancomycin utilization and vancomycin prescribing errors"

Pediatr Infect Dis J 2010 Aug;29(8):707-11

- "Interventions: (1)Targeting the known or suspected pathogens (20%); (2)Consultation (43%); (3)Optimize antimicrobial treatment (33%); and (4)Stop treatment (4%)"

Pediatr Infect Dis J 2008 Feb;27(2):106-11

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Outcome examples…

- "Three of the 84 (3.5%) patients recommended to receive alternative therapy developed an infection not covered by the ASP recommendations or the antimicrobial initially requested by the clinician."
- "18% viewed the program as an obstacle, 70% wanted additional feedback. Compliance was 79%. Costs decreased by 6.4% the 1st year and 2.2% the 2nd year."

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Pediatr Infect Dis J 2008 Feb;27(2):106-11

Monitoring Outcomes…

- Research data linking decreased antibiotic resistance *directly* to ASP difficult…
  - Confounding variables and interventions other than AS that affect resistance prevalence ("bundled" interventions)
  - Limitations of non-randomized study designs
  - Resistance prevalence outcomes = long term measurement

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R.C. Owens Jr / Diagnostic Microbiology and Infectious Disease 61 (2008) 110–128

Daily practice…

A 10-year-old boy, previously well

- 2 days of fever, vomiting, and abdominal pain localized to the right lower quadrant
- CT abdo: perforated appendicitis
- Percutaneous fluoroscopy-guided drainage (cultures)
- Postoperatively, combination of piperacillin sodium and tazobactam sodium, gentamicin sulfate, and metronidazole was started
- 14-day course of parenteral antibiotic therapy (CVP)

Daily practice…

Many *Escherichia coli*, many group F *Streptococcus*, moderate *Bacteriodes fragilis* β-lactamase positive *E Coli*.

Agent	Minimum Inhibitory Concentration	Susceptibility Interpretation
Ampicillin sodium	<8	S
Cefazolin sodium	8	S
Cefepime hydrochloride	<2	S
Cefotetan disodium	<16	S
Ceftazidime	<2	S
Ciprofloxacin hydrochloride	<1	S
Cefotaxime sodium	<4	S
Gentamicin	<1	S
Meropenem	<4	S
Piperacillin and tazobactam	≤16	S
Sulfamethoxazole and trimethoprim (Septra)	<2/38	S
Tobramycin	<1	S

Consider…

"It is interesting to note that only specialists in oncology can prescribe and administer the drugs used for the treatment of cancer but that almost any clinician can prescribe antimicrobial agents.

Perhaps antibiotic prescribing should only be possible by doctors and other health professionals who have been certified as competent, probably after undergoing educational programmes in the field. Gone should be the days when all doctors can prescribe what they like, when they like."

R.C. Owens Jr / Diagnostic Microbiology and Infectious Disease 61 (2008) 110–128

Thank you

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