Costruire una strategia ospedaliera per la prescrizione degli antibiotici. Un obiettivo possibile (..?)

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TODAY'S MENU

What does it mean APPROPRIATE ANTIBIOTIC THERAPY ? ...and

ANTIMICROBIAL STEWARDSHIP ???

Objectives

- Mistakes, errors, or inescapable consequences...?
- Describe antimicrobial stewardship programs, programmatic approaches to minimize inappropriate antimicrobial use and the development of antimicrobial resistance in the hospital setting
- Understand the role of different professionals within programs

Why So Many Mistakes

High number and complexity of drugs

- High number and complexity of syndromes and pathogens
- Poor training in antibiotic use
- Variability over time and place in
 - pathogen prevalence
 - antibiotic susceptibilities
 - antibiotic formularies



« Houston, do we have a problem ? »

CURRENT HEALTHCARE SYSTEM



Control of Antibiotic Resistance



ANTIBIOTIC RESISTANCE IN THE COMMUNITY: FACTORS CONTRIBUTING TO SPREAD IN THE COMMUNITY

- Factors contributing to spread of antibiotic resistance
 - Selection of antibiotic-resistance genes
 - Increase in "high-risk" (immunodeficient) population
 - Prolonged survival of persons with chronic diseases
 - Congregate facilities (e.g., jails, day care centers)
 - Lack of rapid, accurate diagnostic tests to distinguish between viral and bacterial infections
 - Increased use of antibiotics in animals & agriculture

ANTIBIOTIC RESISTANCE IN HOSPITALS: FACTORS CONTRIBUTING TO SPREAD IN HOSPITALS

- Greater severity of illness of hospitalized patients
- More severely immunocompromised patients
- Newer devices and procedures in use
- Increased introduction of resistant organisms from the community
- Ineffective infection control & isolation practices (esp. compliance)
- Increased use of antimicrobial prophylaxis
- Increased use of polymicrobial antimicrobial therapy
- High antimicrobial use in intensive care units

Shales D, et al. Clin Infect Dis 1997;25:684-99.

Dangerous macro-organism: MRMS



Multi-Resistant Medical Specialist







ANTIBIOTIC RESISTANCE:

Physician practices contributing to inappropriate antibiotic use

- Providing antibacterial drugs to treat viral illnesses
- Using inadequate diagnostic criteria for infections that may have a bacterial etiology (simply: blood cultures)
- Providing expensive, broad-spectrum agents that are unnecessary
- Prescribing antibiotics at an improper dose or duration



Resistant to good advice Allergic to professional guidelines Non-compliant with infection control Blind to nosocomial infections Other priorities Missing feeling of accountability

Inappropriate antibiotic therapy

- Inappropriate antibiotic therapy can be defined as one or more of the following:
 - ineffective empiric treatment of bacterial infection at the time of its identification
 - the wrong choice, dose or duration of therapy
 - use of an antibiotic to which the pathogen is resistant



« Houston, we certainly have a problem ...! »

Potential consequences of inappropriate antibiotic therapy

- Inappropriate empiric antibiotic therapy can lead to increases in:
 - mortality
 - morbidity
 - length of hospital stay
 - cost burden
 - resistance selection

My son, if they don't get me you will become multiresistant

Getting it right first !

- Provide optimal empiric therapy based on local microbiology data
- Target dosing and intervals on PK/PD parameters
- Step-down everytime is possible
- Avoid single patient undertreatment and hospital-wide overtreatment
- Shorten duration

The antimicrobial therapy puzzle



Antimicrobial drugs & pattern of activity I.

• HYDROPHILIC

- β-lactams
- Glycopeptides
- Carbapenems
- Aminoglycosides
- Unable to cross cell membrane
- Inactive against intracellular pathogens
 Usually renal clearance

• LIPOPHILIC

- Oxazolidinones
- Rifampin
- Quinolones
- Azalides
- Able to cross cell membrane
- Active against intracellular pathogens
- Usually liver metabolism

Antimicrobial drugs & pattern of activity II.

- Time-dependent
- β-lactams
- Glycopeptides
- Oxazolidinones
- Carbapenems
- Usually no PAE
- Stable, unfloating concentrations over 24 hrs.

- Concentration-dependent
- Aminoglycosides
- Rifampin
- Quinolones
- Azalides
- High PAE
- Peak over the MIC, regardless of timing

Meropenem IV





Time-dependent antimicrobials

"Dynamic" MICs achieved with optimized therapy

Drug	Daily dose	MIC
Pip/tazo	18 g	60
Pen G	18 MU	9
Amoxicillin	12 g	21
Oxacillin	12 g	1
Ampicillin	12 g	28
Meropenem	12 g	16





How to read (and understand) antimicrobial susceptibility testing. II.

Ciprofloxacin & *Pseudomonas aeruginosa*MIC < 1 mg/L SUSCEPTIBLE

- MIC < 0.3 mg/L susceptible 400 mg x 2
- MIC < 0.6 mg/L susceptible 600 mg × 2
- MIC > 0.6 mg/L susceptible



COMBO!

RISK ADJUSTED APPROACH to CHOOSE "OPTIMAL" THERAPY

everity of illness (SIRS / PIRO scale) Organ dysfunction (SOFA score) ge & Co-morbidities (Mc Cabe score) ommunity vs Hospital acquisition ite-related Nicroorganism-related esistance-related

PK/PD knowledge Physiopathological status Site of infection

DRUGS' CHOICE

REGIMENS' CHOICE

Do your medical policies and procedures reflect the times?

ANTIMICROBIAL STEWARDSHIP

 A system of informatics, data collection methods, personnel, and policy / procedures which promotes the optimal selection, dosing, and duration of therapy for antibiotics

The Why of Antimicrobial Stewardship

- Antimicrobial use is characterized by
 - Poor quality
 - High quantity
- This leads to
 - Poor clinical outcomes
 - Antimicrobial resistance
 - Excessive costs

ANTIMICROBIAL STEWARDSHIP: GOALS

- Optimal selection, dose, and duration of an antimicrobial therapy that results in the best clinical outcome for the treatment of infection, with minimal toxicity to the patient and minimal impact on subsequent development of resistance
 - Reduce morbidity and mortality
 - Reduce length of stay
 - Reduce health care expenditures (without compromising quality of care)

• Wow ! That's also APPROPRIATE THERAPY..!

STRATEGY & VISION

• Transversal project at the institutional level

• Tight collaboration between all stakeholders

- Infectious diseases
- Clinical microbiology
- Clinical pharmacology & pharmacy
- Infection control
- Clinical informatics

KEY ISSUES - The *five* commandments...

• Learn

- Surveys
- Detect
 - Audits
- Intervene
 - Decision support & prevention
- Teach
 - Training & education
- Evaluate
 - Outcome assessment



MISSION STATEMENT

- Improve quality and adequacy of antibiotic use
- Decrease adverse effects due to misuse
- Increase medico-economic efficiency
- Implement sustained solutions
- Evaluate the long term effects of the program

Antibiotic Prescribing Policy & Practice in Acute Hospitals



What do ID physicians ask to the Microbiologist of the new millennium?

Epidemiological responsibility



hospital-wide and individual Unit Ecology hospital-wide and critical settings burden of resistances reliable MICs and information about trends

Routine collection, tabulation, analysis and feedback of information on the occurrence of Resistance



Essential before planning any intervention

Work closely with the Microbiologist

- Role of microbiologist
 - Provides patient-specific cultures and susceptibility data to optimize individual antimicrobial management
 - Assists infection control efforts in the surveillance of resistant pathogens and in the molecular epidemiologic investigation of outbreaks
 - Critical role in the timely identification of microbial pathogens and the performance of susceptibility testing
 - (please, see overleaf for his/her responsibilities....)

Work closely with the Microbiologist

Responsibilities of microbiologist

- Analyze and present data at least once per year
- Use a sufficient number of isolates to assure accurate data
- Perform and report quantitative and qualitative susceptibility testing
- Help drive PK/PD approach to tailored antimicrobial therapy
- Conduct group review of data

ID Pharmacist Specialist

Responsibilities

- Provides cost-effective pharmaceutical care to patients receiving select/targeted antimicrobial therapy
- Discuss antimicrobial order changes with ID physician or prescriber
- Document changes and inform others of those changes
- Provide PK/PD services as required (....)
- Provide in-service programs to all hospital staff
- Review (yearly?) antibiograms with appropriate individuals on a regular basis

ID Pharmacist Specialist

- Responsibilities (continued...)
 - Provide financial forecasts for the ID physician and the Dept. of Pharmacy for new and investigational drugs and related pharmaceuticals
 - Provide presentations, publications at the local, regional, and national level
 - Conduct collaborative research or plan to test the effectiveness of new methods of antimicrobial control/restriction/reporting that may increase the effectiveness of antimicrobial stewardship

...are you happy with the new workload...??

SUGGESTED INTERVENTIONS ON MONITORING

Retrospective/prospective data on antimicrobial use

- Ecologic data
- Individual patient-level data
- Evaluation of direct costs of antibiotic therapy
- Monitoring of antimicrobial resistance trends, feed-back to prescribers
- Adherence to guidelines
- Adherence to antibiogram & culture results
- ..others..?

SUGGESTED INTERVENTIONS ON DECISION SUPPORT

• Guided choices for empirical treatment

- Clinical, microbiological and economic considerations
- Reduction of antibiotic treatment
 - Duration
 - De-escalation with the help of microbiology results
 - Intravenous to oral switch
- Formulary restrictions on expensive, non-listed, or endangered antimicrobial drugs

ANTIMICROBIAL STEWARDSHIP: INTERVENTIONS

Antimicrobial restrictions and controls

- Assistance in antimicrobial dosing
 - Feedback to MD to optimize therapy
 - Immediate feedback when informatics detects antimicrobial/pathogen mismatch
 - Identify candidates for early IV to PO switch
- Automatic Stop Orders
- Therapeutic Substitutions
- Cycling (Benefit unproven)



(modified) MacDougall C and Polk RE. Clin Microbiol Rev. 2005;18:638-56.

Formulary Restrictions

• Free available drugs

- Fluoroquinolones
- 3rd generation cephalosporins
- Imipenem (until 12.08)
- Most β-lactams
- Macrolides
- Aminoglycosides
- Tazobactam/piperacillin
- Fluconazole



- On approval drugs
 - Ceftazidime & Cefepime
 - Meropenem & Ertapenem
 - Glycopeptides
 - Aztreonam
 - Antifungals*
- Restricted drugs
 - Linezolid & Q-D
 - Daptomycin
 - Tygecyclin
 - Antifungals
 - Clindamycin
 - Rifampin
 - Any new one

Unit for Hospital Antimicrobial Chemotherapy (UHAC) Bolzano Central Hospital Project for Antimicrobial Stewardship Program

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Antimicrobial Stewardship Program May Help Reduce Antimicrobial Resistance in ICU

Pagani L, et al. Clin Microbiol Infect 2008

- Gennaio 2003 dicembre 2007: sorveglianza delle sensibilità dei principali patogeni nosocomiali isolati da campioni clinici di pz ricoverati in ICU da più di 48-72 ore.
- Sangue, broncoaspirati/BAL, ferita chirurgica, urina, liquor, drenaggi
 - a) eliminazione della profilassi con 3rd-Ceph in pazienti critici all'entrata in ICU
 - b) impostazione di terapia empirica per sospette infezioni acquisite in ICU sulla base dell'epidemiologia delle R locali e di elementi di PK/PD
 - c) rivalutazione regolare della terapia alla luce dei dati microbiologici, con orientamento alla "de-escalation" e alla "short course"

RESULTS (I) Antimicrobial Consumption

ATB	2002-DDD	2006-DDD	%
VAN	390	103	-73.3
TEC	100	5	-95
CIP	1136	624	-45
AMK	290	20	-93
CAZ	70	15	-78.6
AMP/SB	1887	798	-57.7
PIP/TZ	366	369	-
MEM	25	405	+1620
LIN	156*	760	+487

MRSA and ICU



Pagani L, et al. Infect Control Hosp Epidemiol 2008; in press

RESULTS (II)

S. aureus susceptibilities

Antibiotico	% S	% S	% R
	2002	2006	2006
PEN	15.2	24.3	75.7
ΟΧΑ	65.5	84.2	15.8
CIP	65.7	84.3	15.7
CLD	69.7	93.7	6.3
VAN	100	100	_
TEC	100	100	_

RESULTS (III)

P. aeruginosa Susceptibilities

Antibiotico	% S 2002	% S 2006	% R 2006
CIP	84.4	83.8	16.2
AMK	93.6	100	0
CAZ	82.7	90.3	9.7
PIP/TZ	88.8	93.5	6.5
GEN	71.9	83.8	16.2
CFP	87.5	93.5	6.5
MEM	83.8	83	17

Antimicrobial Stewardship Program is self-supporting and does not require extra costs (in the very first moments....)

- Bolzano Intensive Care Unit
 - 18 bed-, general ICU
 - Expenditure for antimicrobials:
 - € 109,627 in 2002
 - € 115, 492 in 2007

p < ?????





Bolzano hospital-wide integrated projects

Carried out:

• Ongoing:

- ICU
- Surgical prophylaxis
- Pneumology
- Ophthalmology
- Hematology and BMT (.....)
- Central venous catheters
- Clostridium difficile
- Single ward epidemiology

- Surgical therapy
- TDM
- Urology
- Orthopedics
- Pediatrics & Pediatric surgery
- Infection Control (WHO)
- MIC reports
- POC
- Geriatrics & LTCFs

Antimicrobial stewardship programs reviews and tips

- Dellit TH, Owens RC, McGowan JE, Jr., et al.
- IDSA and the SHEA guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77
 - MacDougall C, Polk RE.
- Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev 2005;18:638-56
 - Lesprit P, Brun-Buisson C.
- Hospital antibiotic stewardship. Curr Opin Infect Dis 2008;21:344-9

Navigating the Web in Search of Resources on Antimicrobial Stewardship Programs in Health Care Institutions

- The Center for Diseases Control website <u>http://www.cdc.gov/drugresistance/healthcare/default.htm</u>
- The Healthcare Infection Control Special Interest Group (HICSIG) website http://www.asid.net.au/hicsigwiki/index.php?title=Antibiotic_stewa rdship_programs#Guides
- The Nebraska Medical Center website <u>http://www.nebraskamed.com/careers/education/asp/index.aspx</u>
- The Washington University in St. Louis and Barnes-Jewish Hospital <u>http://id2.wustl.edu/~casabar/antibiotics.html</u>
- The "Antimicrobial Management Program" has its own direct link http://www.uphs.upenn.edu/bugdrug/ within The University of Pennsylvania Health System Web site <u>http://pennhealth.com</u>

Pagani L, et al. *Clin Infect Dis* 2008; in press

Future Basis of Antibiotic Use in Clinical Practice

• Get it Right Up Front (aggressive approach)

- Reduce infection related morbidity and mortality associated with inappropriate antimicrobial therapy
- Optimize PD profile of agents utilized
- De-escalation
 - Streamline therapy once susceptibility data are available
 - Reduce prolonged and unnecessary therapy
- Costs saved by avoiding treatment failure greater than costs spent by on antimicrobial therapy

• PREVENT INFECTIONS

- Hand hygiene and educational programs
- Surveillance projects
- Environmental care

• MORE APPROPRIATE ANTIMICROBIAL PRESCRIPTION

- Avoid undertreatment of single patients and overtreatment of population
- Hospital formulary for surgery prophylaxis
- Reduction of useless combination therapy
- Cycling?
- Formulary restrictions for endangered or newer drugs
- Unit/hospital-tailored guidelines
- Epidemiological and starring role of microbiology

CONCLUSIONS

- The changing healthcare environment is diminishing the boundaries between traditional community and hospital-acquired infections.
- Inappropriate antimicrobial use and failure to fully implement infection control recommendations are leading to the emergence of antimicrobial-resistant pathogens.
- Increased collaboration between clinicians, infectious disease, infection control and microbiology personnel, public health authorities, and private industry will be needed to reduce antimicrobial use, improve infection control, and prevent the further emergence of antimicrobial-resistant pathogens.

Principles for prescribing

- Identification of bacterial infection by optimized diagnosis
- Severity assessment
- Recognition and incorporation of local resistance data
- Targeting bacterial eradication (or maximal reduction in bacterial load)
- Use of pharmacodynamic (PD) indices to optimize choice and dosage
- Objective assessment of true (overall) costs of resistance and related treatment failure

Ball et al. J Antimicrob Chemother 2002; 49:31-40

"Knowledge is power."

Sir Francis Bacon, Religious Meditations; Of Heresies, 1597



What Is A Bundle?

- A structured way of improving the processes of care and patient outcomes
- A small, straightforward set of practices generally three to five — that, when performed collectively and reliably, have been proven to improve patient outcomes.
- The changes in a bundle are NOT new; they are well established best practices, but they are often not performed uniformly, making treatment unreliable, at times idiosyncratic.
- A bundle ties the changes together into a package of interventions that people know must be followed for every patient, every single time.

Bundle Elements

• The changes are *all necessary and all sufficient*,

- If you have four changes in the bundle and you remove any one of them, you wouldn't get the same results
- The changes are all evidence-based
 - Level 1 scientific evidence.
 - Accepted, well-established practice.
 - There should be no controversy involved, no debate or discussion of bundle elements.
 - A bundle focuses on how to deliver the best care not what the care should be.

Bundle Elements

- The changes in a bundle are clear-cut and straightforward.
 - Involve *all-or-nothing measurement*.
 - Successfully completing each step is a simple and straightforward process.
 - It's a "yes" or "no" answer: "
 - Yes, I did this step and that one; no, I did not yet do this last one."
 - "Yes, I completed the ENTIRE bundle, or no, I did not complete the ENTIRE bundle."

 Bundle changes occur in the same time and space continuum: at a specific time and in a specific place, no matter what.

Cooke FJ. The missing care bundle: antibiotic prescribing in hospitals. Int J Antimicrob Agents. 2007; 30:25.

PRSP: Interventions to Improve Antimicrobial Use Rural Alaska Villages



- Studied children <5 yrs old, 3400 persons
- 3 rural regions: 1 study
 2 control
- Educational intervention to parents and providers on judicious antibiotic use in study region
- Focused on respiratory tract infections

Peterson, ICAAC, 1999

...for the Study of Antimicrobial Resistance in Nosocomial Pathogens:

NO ESKAPE !!

- Enterococcus faecium
- Staphylococcus aureus
- Klebsiella pneumoniae
- Acinetobacter baumannii
- Pseudomonas aeruginosa
- Enterobacteriaceae

Rice LB. J Infect Dis 2008;197:1079