

ASP: solo letteratura o pratica clinica ?

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Presidente GISA

Disclosures 2018-2019

- **Advisory Board:** Angelini, MSD, Nabriva, Pfizer
- **Speaker/chairman:** Angelini, MSD, Pfizer
- **Events Sponsorship:** Angelini, Gilead, Pfizer, MSD, Shionogi, Menarini, ViiV, Correvio, Janssen, Nordic Pharma, BioMerieux, Bayer, Thermofisher
- **Ongoing research protocol:** Angelini, MSD, Shionogi, Pfizer

Drivers della AMR e governo della terapia antimicrobica

- L'emergenza di microrganismi MDR è influenzata dalla pressione selettiva degli antibiotici sulla flora intestinale: necessità di appropriatezza prescrittiva
- Programmi che controllino l'uso della terapia antimicrobica: **ANTIMICROBIAL STEWARDSHIP**
- La diffusione crociata dei microrganismi MDR è condizionata dall'osservanza delle buone pratiche assistenziali: **INFECTION CONTROL**

Antimicrobial Stewardship

“Programma o serie di interventi diretti al

***AS: governo della terapia
antimicrobica***

Tamma PD, Cosgrove SE. Infect Dis Clin N Amer 2011; 25: 245-60

Antimicrobial Stewardship Program Goals

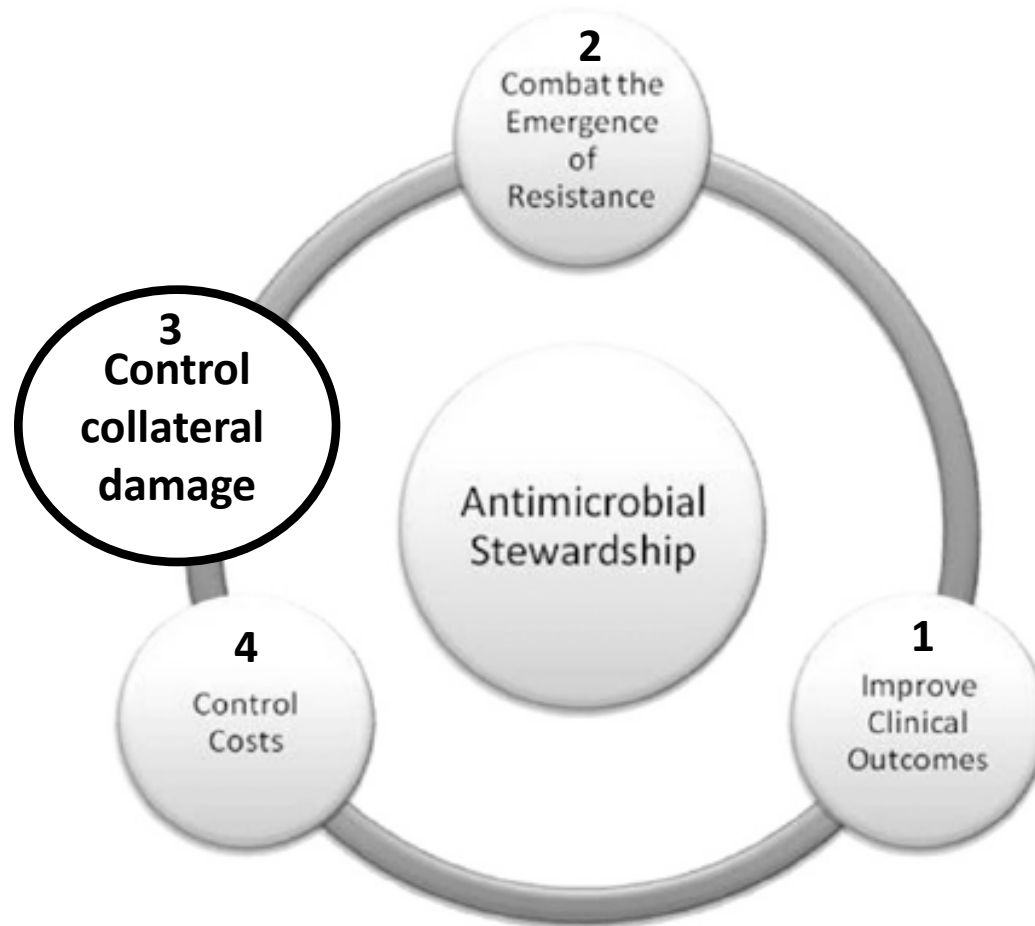


Figure 1. Goals that antimicrobial stewardship strives to achieve.

Lawrence KL et al. *Am J Respir Crit Care Med* 2009; 179: 434–438.

ASP: Process & Outcome Measures

Process Measures

Excess days of therapy (ie, unnecessary days of therapy avoided based on accepted targets and benchmarks)^a

Duration of therapy

Proportion of patients compliant with facility-based guideline or treatment algorithm^a

Proportion of patients with revision of antibiotics based on microbiology data

Proportion of patients converted to oral therapy

Outcome Measures

Hospital length of stay

30-day mortality






Unplanned hospital readmission within 30 d

Proportion of patients diagnosed with hospital-acquired *Clostridium difficile* infection or other adverse event(s) related to antibiotic treatment^a

Proportion of patients with clinical failure (eg, need to broaden therapy, recurrence of infection)

List of interventions considered as part of antimicrobial stewardship

Table 1. List of interventions considered as part of antimicrobial stewardship^{9,11,12}

Intervention*	Description/comment	Healthcare setting
Formulary restriction 	Antibiotics may be prescribed only: <ul style="list-style-type: none"> • For certain approved clinical indications • By certain physicians (i.e., infectious diseases specialists) 	Inpatient/outpatient
Drug preauthorization	Permission (from ASP team member or infectious diseases specialist) required for release of certain antibiotics. Often implemented together with formulary restriction.	Inpatient/outpatient
Prospective audit and feedback	Case review by trained ASP team member and feedback of recommendations if reviewed antibiotics are deemed to be inappropriately prescribed. Labor-intensive.	Inpatient
Prescriber education 	More effective as a supplementary strategy to other interventions.	Inpatient/outpatient
Patient education	Usually focus groups or mass media campaigns.	Outpatient
Clinical guidelines 	Treatment protocols for various infections – may be institution-specific	Inpatient/outpatient
Clinical decision support systems	Information technology systems for improving antibiotic prescription. Requires existing electronic records and electronic prescribing system to be effective.	Inpatient/outpatient
Point of care diagnostic tests 	Mostly undergoing research evaluation. Diagnosis of non-bacterial etiologies may help reduce antibiotic prescription.	Inpatient/outpatient
Microbiology laboratory susceptibility reporting 	Selective reporting of susceptibility profiles for positive cultures may dramatically alter prescribing patterns of physicians.	Inpatient/outpatient
Antimicrobial cycling	Substitution of selected antibiotics over pre-defined periods. Little clear evidence for efficacy. ¹²	Inpatient

Antimicrobial stewardship

Azienda Ospedaliera Universitaria Pisana

- **Protocolli di profilassi perioperatoria**
- **ID POOL esclusivamente dedicato alle consulenze**
- **Vincolo sulle prescrizioni di alcuni farmaci**
- **Alert system microbiologico**
- **Report di resistenza aggregati per gli isolati da emocoltura**
- **Report sul consumo di antibiotici per aree di degenza e reparti**
- **Formazione sulla sepsi, su emergenze infettivologiche e infezioni ospedaliere**

Antimicrobial stewardship

Azienda Ospedaliera Universitaria Pisana

- Alert microbiologici per microorganismi sentinella:
 - *Candida* da emocoltura
 - *C. difficile*
 - CRE (fenotipo e genotipo)
 - *P. aeruginosa*
 - *A. baumannii*
 - Pneumococco e Legionella (urine)
 - TBC
 - Influenza, morbillo, parotite, parvovirus, etc.

Antimicrobial stewardship

Azienda Ospedaliera Universitaria Pisana

Gruppo multidisciplinare AID
(antibiotic stewardship, infection control,
diagnostic)
su delibera regionale e aziendale

Livelli prescrittivi

- Terapia Intensiva e Ematologia
 - Autonomia prescrittiva
 - Altri reparti
 - Restrizione della prescrizione di antibiotici e antifungini selezionati (modello *front-end*)
 - Necessità di ID consultation
 - Farmaco fornito per 5 giorni, salvo diversa indicazione dell' infettivologo
- NB:*** per i farmaci soggetti a scheda AIFA al momento è necessaria la consulenza infettivologica per tutti i reparti

Consulenza infettivologica

- Su chiamata del reparto (mail o telefono)
- Intervento sistematico settimanale in UTI Trapianti e Centro Ustioni
- WhatsApp...

MODULO DI CONSULENZA INFETTIVOLOGICA

Compilazione a cura del Reparto

U.O. RICHIEDENTE _____ CENTRO DI COSTO _____ TEL _____ FAX _____

MEDICO RICHIEDENTE _____ STABILIMENTO _____ EDIFICIO _____ PIANO _____ LETTO _____

NOME E COGNOME _____ DATA DI NASCITA ____/____/____ SDO _____ PESO KG _____

1) INFORMAZIONI PER LA U.O. MALATTIE INFETTIVE

DATA RICHIESTA _____ URGENTE ☐ SI ☐ NO ☐

A LETTO DEL DEGENTE ☐ AMBULATORIALE ☐

QUESITO CLINICO _____

1) TRASMETTERE RICHIESTA CONSULENZA ALLA U.O. MALATTIE INFETTIVE AL FAX N. 6747

2) INFORMAZIONI PER LA U.O. FARMACEUTICA

RICHIESTA FARMACI (GE4) N. _____

2) TRASMETTERE CONSULENZA CON RICHIESTA FARMACI ALLA U.O. FARMACEUTICA AL FAX N. 2309

TIMBRO E FIRMA

Compilazione a cura del consulente

BREVE RELAZIONE E RACCOMANDAZIONI

IPOTESI DIAGNOSTICA _____

Farmaci prescritti	Posologia

Consulenza valida per _____ giorni di terapia (5 giorni se non diversamente specificato).

Prima prescrizione ☐ Prosecuzione di terapia ☐

Terapia empirica ☐ Terapia mirata ☐ Switch ev-os ☐ De-escalation ☐

Isolati e localizzazioni _____

CLEARANCE CREATININA ☐ >50 MG/DL ☐ 10-50 MG/DL ☐ <10 MG/DL

DATA _____ ORA _____

TIMBRO E FIRMA

Farmaci sottoposti a restrizione

- **Antibiotici**

- Levofloxacin EV
- Teicoplanina, daptomicina, linezolid, tedizolid*
- Dalbavancina*
- Tigeciclina
- Colistina
- Fosfomicina
- Meropenem, imipenem ed ertapenem
- Ceftarolina* e ceftobiprolo,
- ceftolozane/tazobactam*, ceftazidime/avibactam*
- Fidaxomicina*

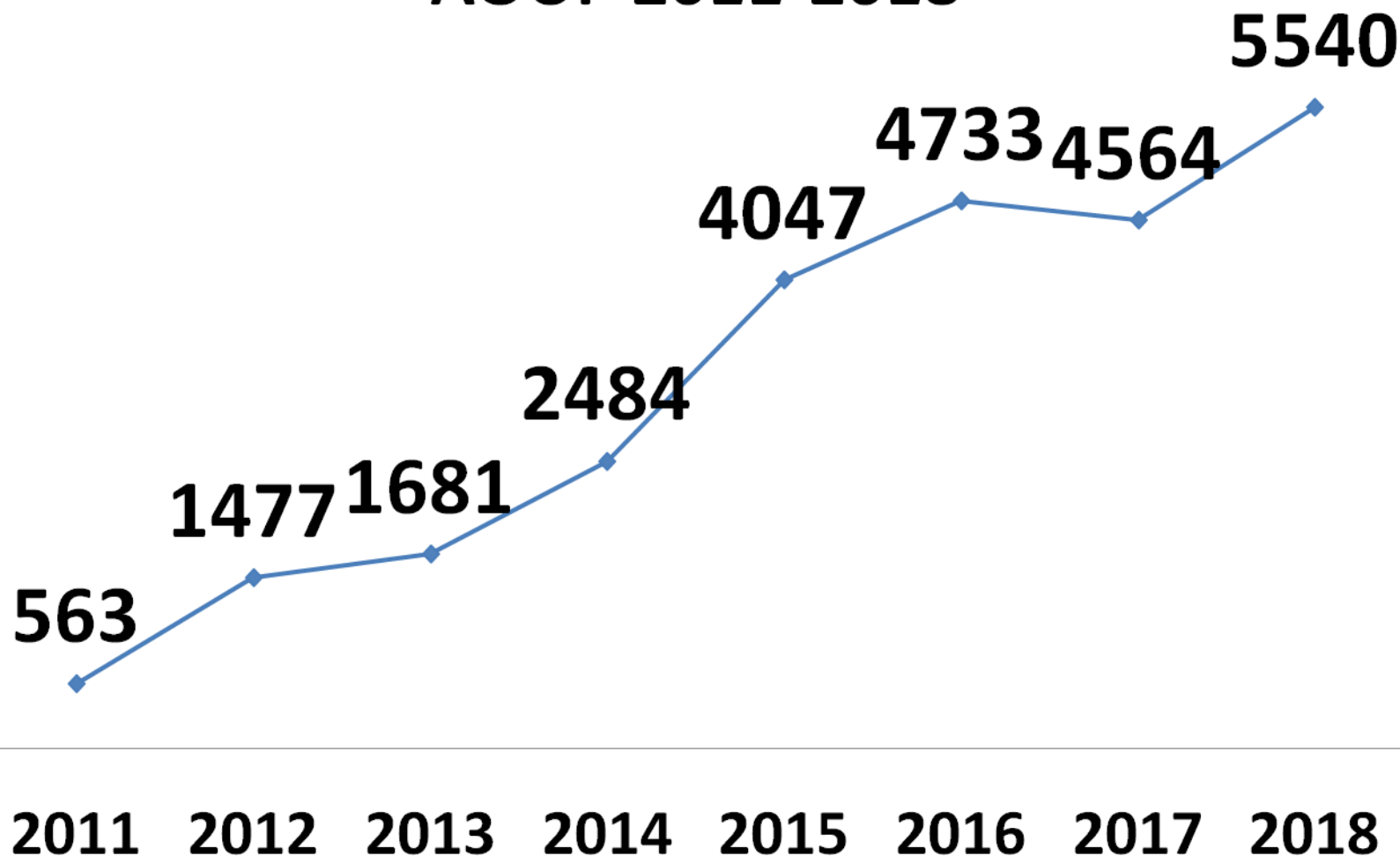
- **Antifungini**

- Voriconazolo e isavuconazolo
- Amfotericina B
- Echinocandine

* Scheda AIFA

Consulenze infettivologiche

AOUP 2011-2018



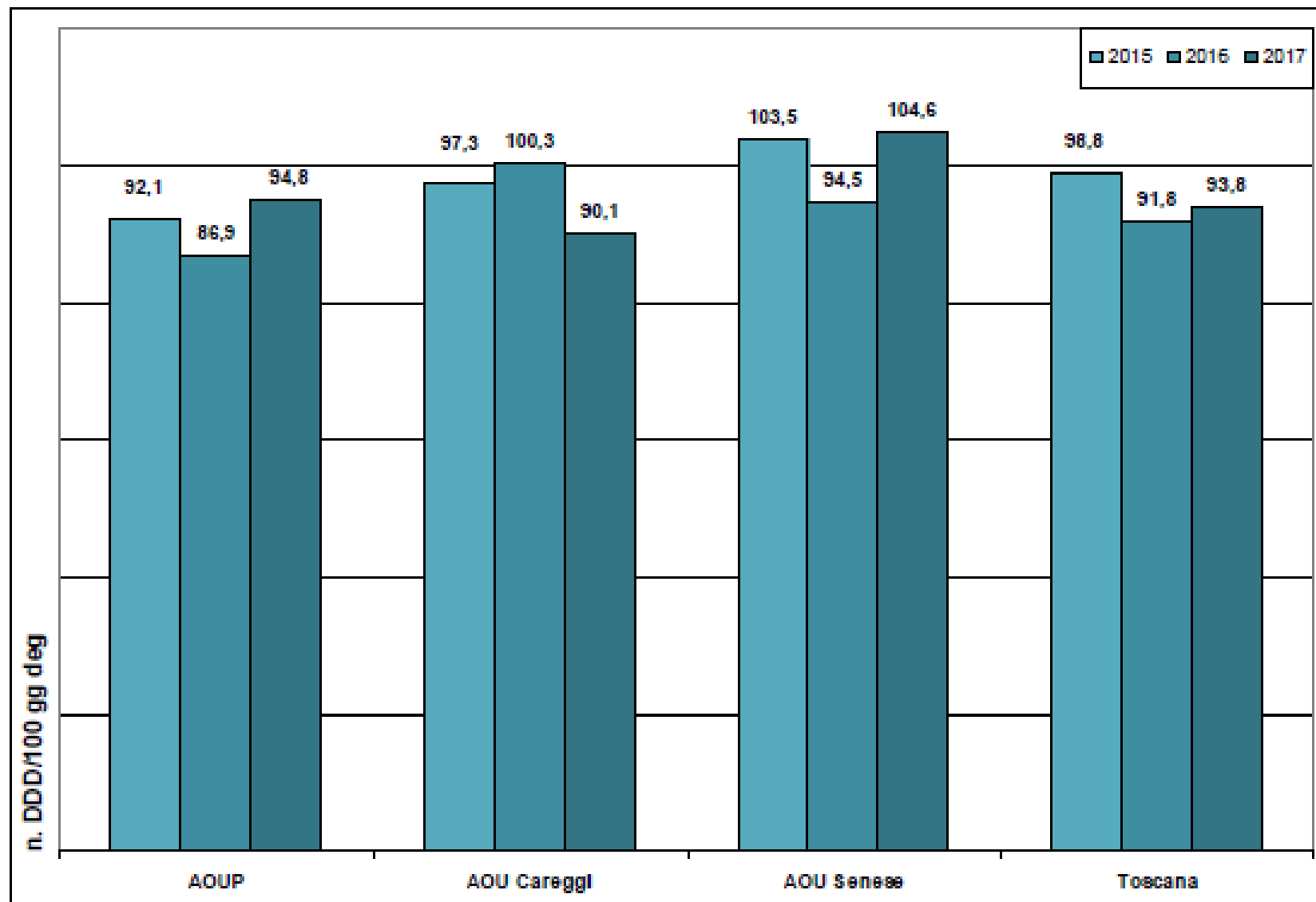
ASP rationale

- The challenge with antimicrobial prescribing is the need to balance two conflicting goals:
 1. the provision of therapy that is adequate to treat documented or presumed infection, and
 2. the minimization of antimicrobial use to avoid adverse drug events (e.g., *Clostridium difficile* infection and allergy) and the emergence of antimicrobial resistance, and to reduce costs.

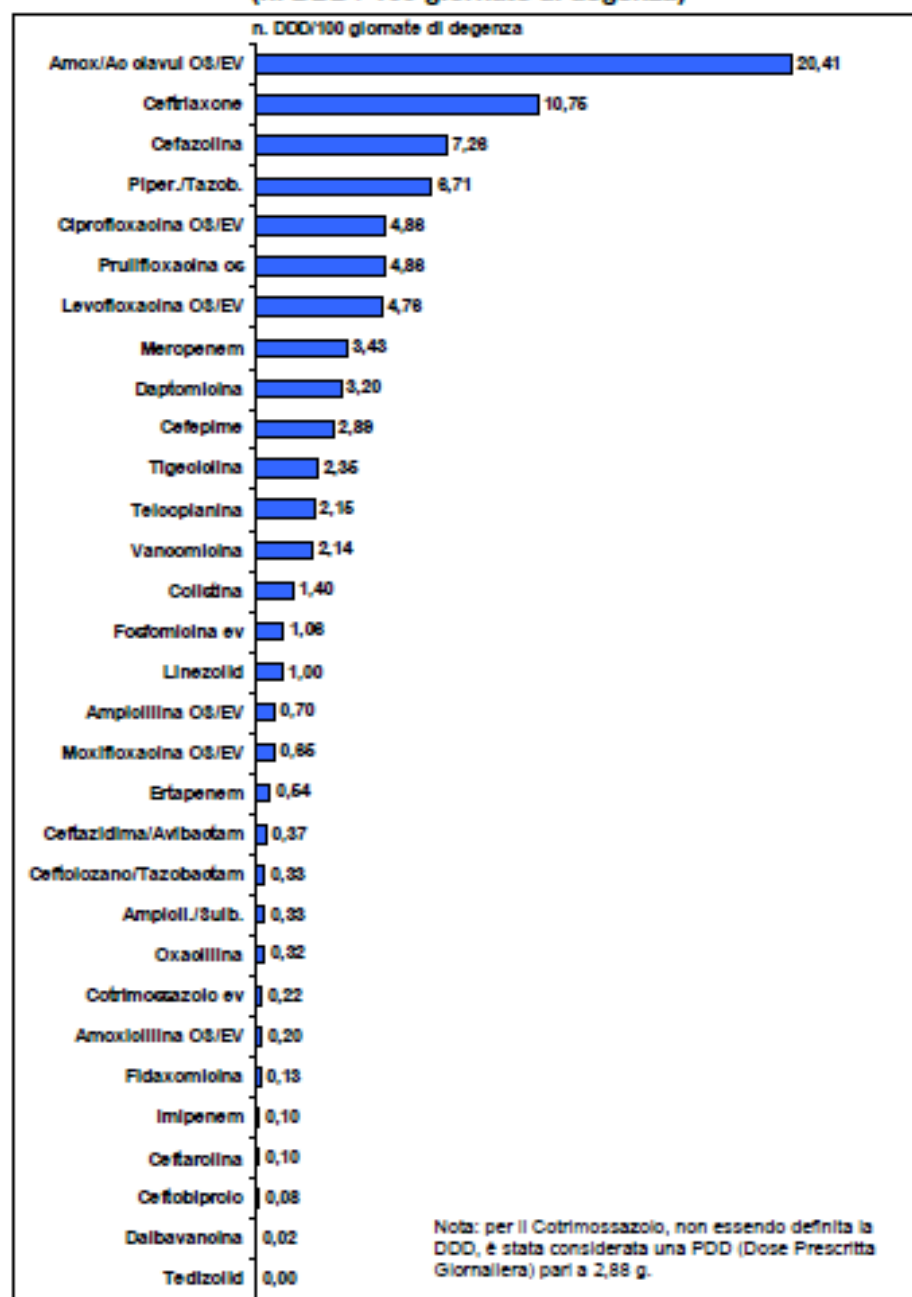
Primary ASP metrics

- **Antimicrobial use**
- **Microbiological resistance**
- **Clinical outcomes**

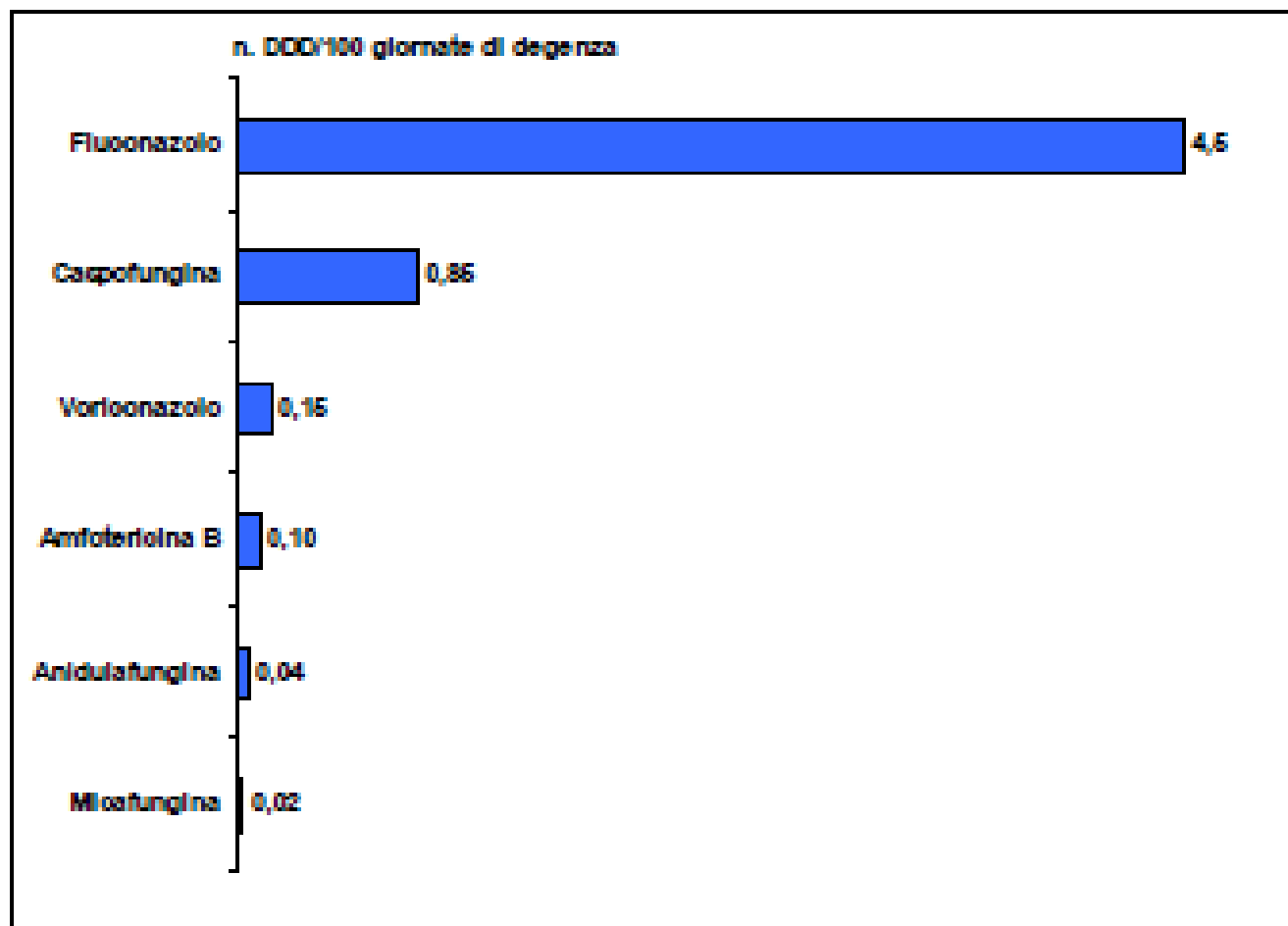
1) Consumo complessivo di antibiotici per uso sistemico in AOUP e in Toscana negli anni 2015- 2017 (n. DDD / 100 giornate di degenza)
Fonte ARS



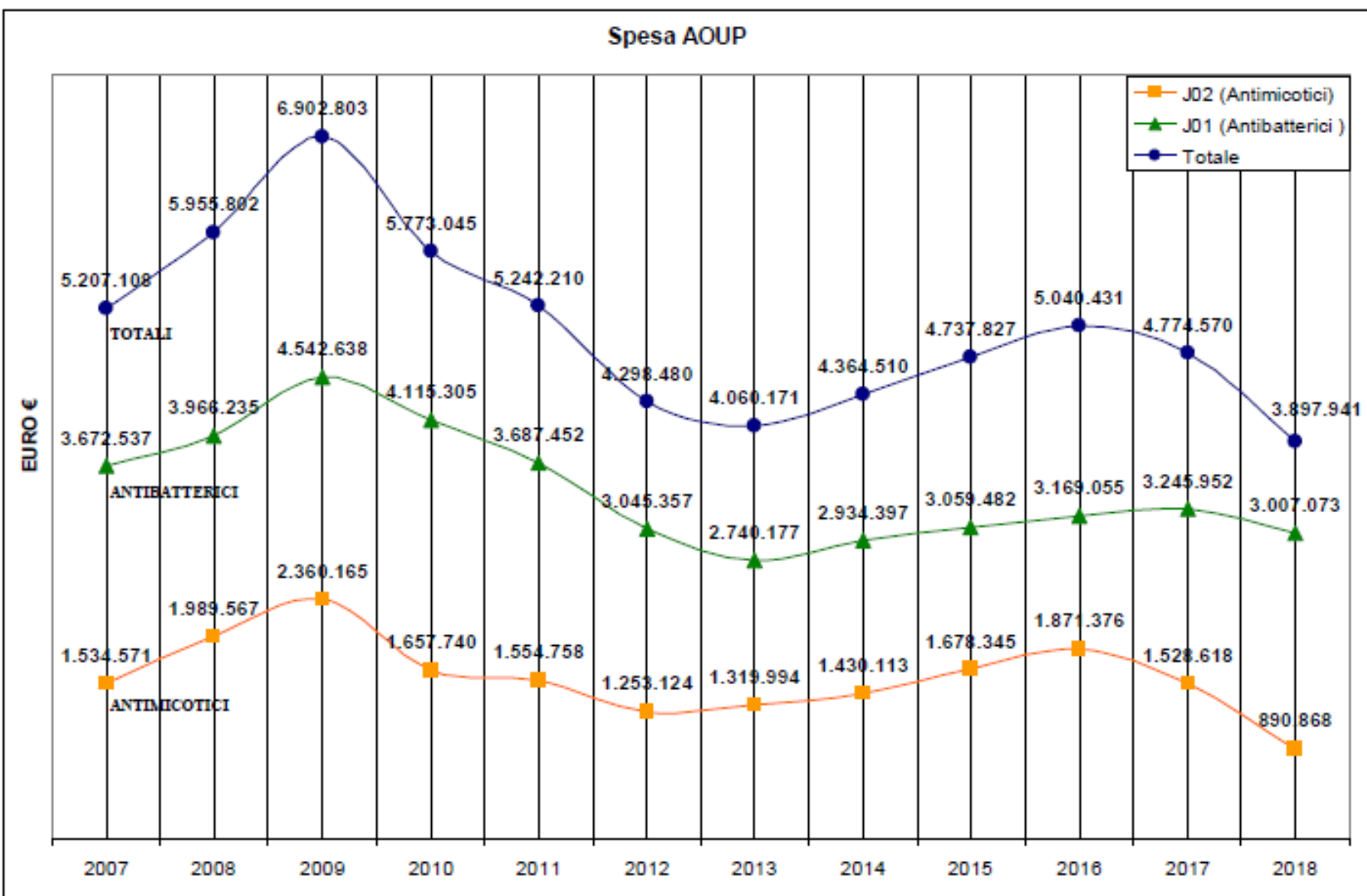
**2a) Principali antibatterici consumati in AOUP nell'anno 2018
(n. DDD / 100 giornate di degenza)**



2b) Principali antifungini consumati in AOUP nell'anno 2018
(n. DDD / 100 giornate di degenza)



7) Spesa complessiva antibatterici e antifungini AOUP anni 2007 - 2018



ASP: the role of ID consultation

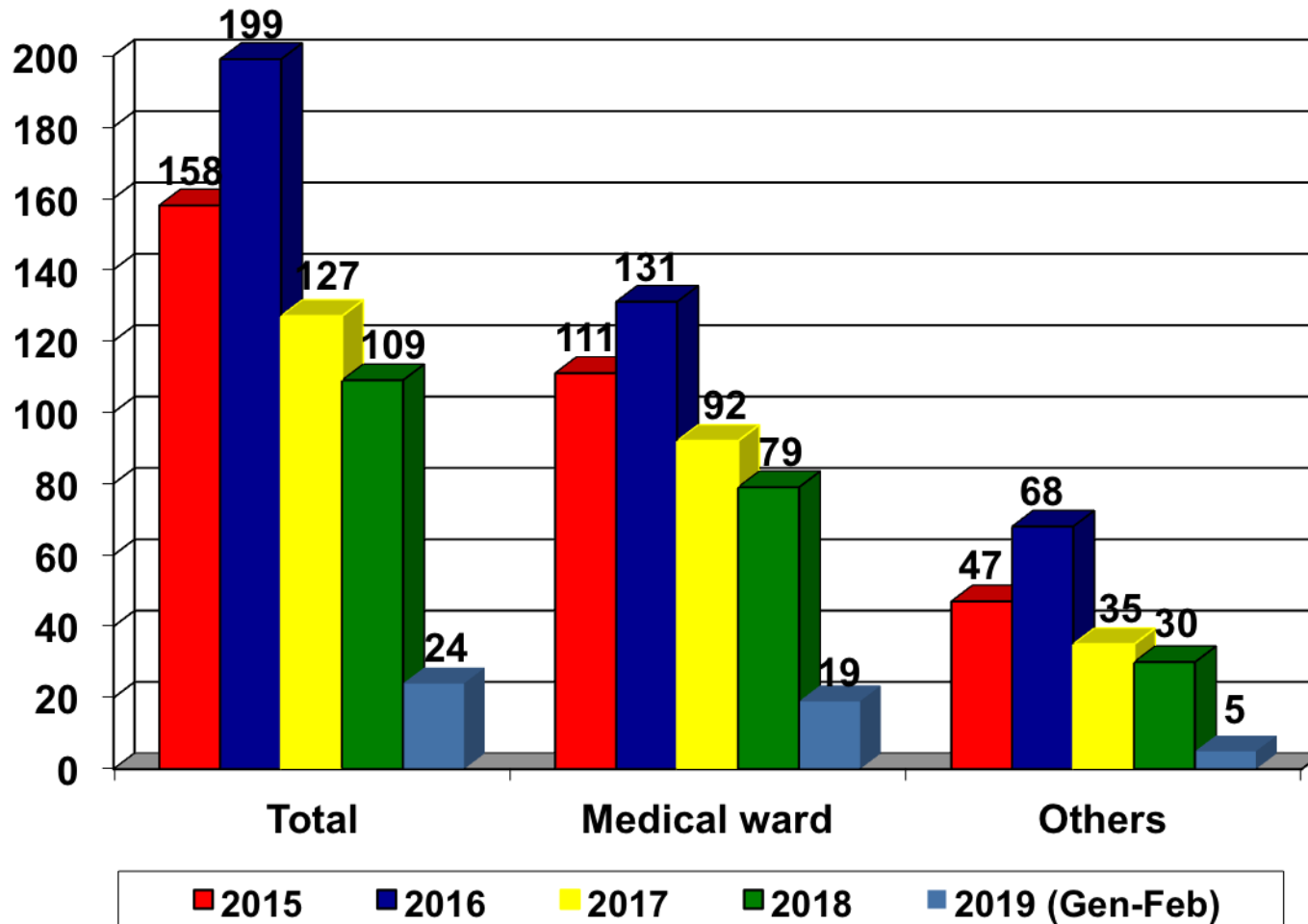
Infectious Diseases Specialty Intervention Is Associated With Decreased Mortality and Lower Healthcare Costs

Steven Schmitt,¹ Daniel P. McQuillen,² Ronald Nahass,³ Lawrence Martinelli,⁴ Michael Rubin,⁵ Kay Schwebke,⁶ Russell Petrak,⁷ J. Trees Ritter,⁸ David Chansolme,⁹ Thomas Slama,¹⁰ Edward M. Drozd,¹¹ Shamonda F. Braithwaite,¹¹ Michael Johnsrud,¹² and Eric Hammelman¹¹

¹Department of Infectious Diseases, Medicine Institute, Cleveland Clinic, Ohio; ²Center for Infectious Diseases and Prevention, Lahey Hospital & Medical Center, Tufts University School of Medicine, Burlington, Massachusetts; ³ID Care, Hillsborough, New Jersey; ⁴Covenant Health, Lubbock, Texas; ⁵Divisions of Clinical Epidemiology and Infectious Diseases, University of Utah School of Medicine, Salt Lake City; ⁶OptumInsight, Eden Prairie, Minnesota; ⁷Metro ID Consultants, LLC, Burr Ridge, Illinois; ⁸French Hospital Medical Center, San Luis Obispo, California; ⁹Infectious Disease Consultants of Oklahoma City, Oklahoma; ¹⁰Indiana University School of Medicine, Indianapolis, Indiana; ¹¹Data Analytics, and ¹²Health Economics and Outcomes Research, Avalere Health, Washington, D.C.

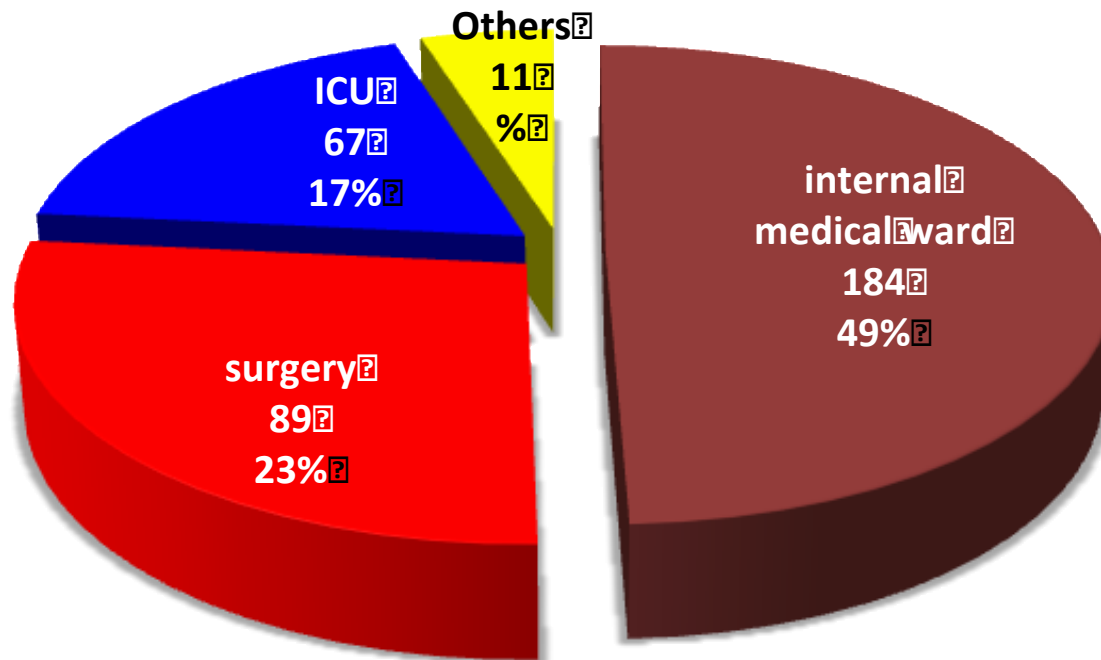
Clostridium difficile infections

Pisa tertiary-care, un. hospital (1180 beds)



Candidemie 2012-2014

Pisa Hospital: 341 episodes



Candidemie 2012-2014

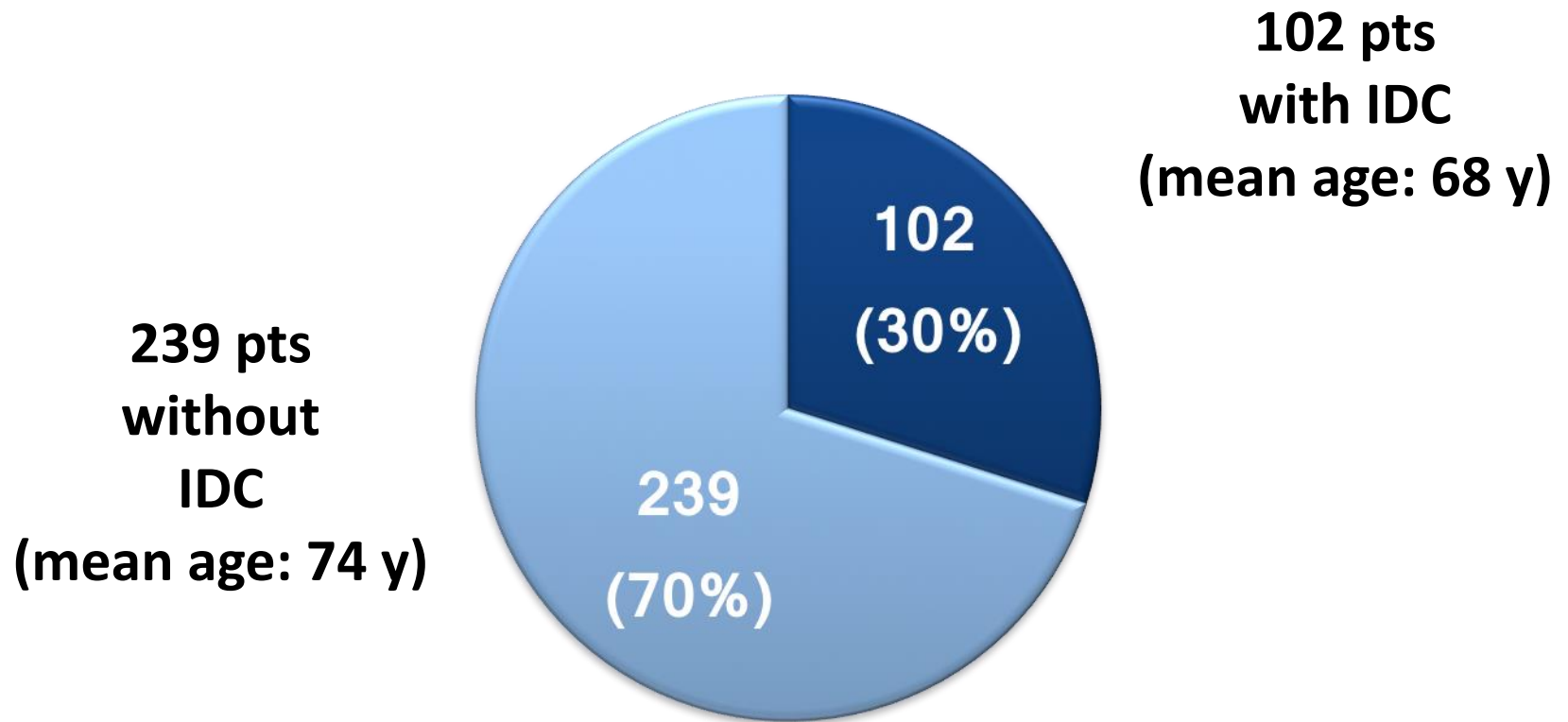
Pisa Hospital: 341 episodes

Patients	341	
<i>C. albicans</i>	188	(50%)
<i>C. parapsilosis</i>	98	(26%)
<i>C. glabrata</i>	38	(10%)
<i>C. tropicalis</i>	23	(6%)
<i>C. krusei</i>	8	
Others	22	

CANDIDEMIE 2012-2014 AOUP: 341 EPISODI

PAZIENTI

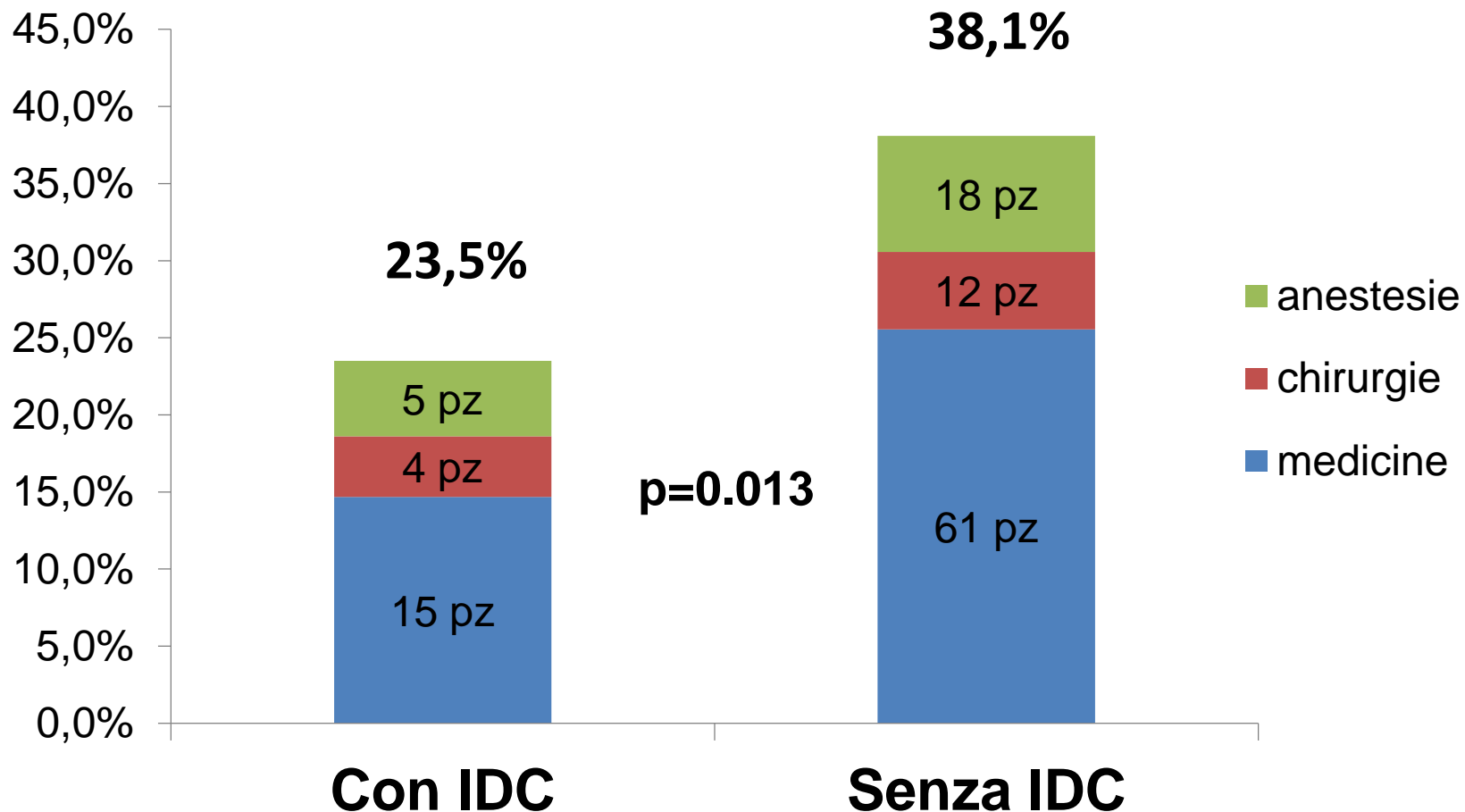
■ IDC ■ NO IDC



Pisa Hospital 2012-2014

341 CANDIDEMIA

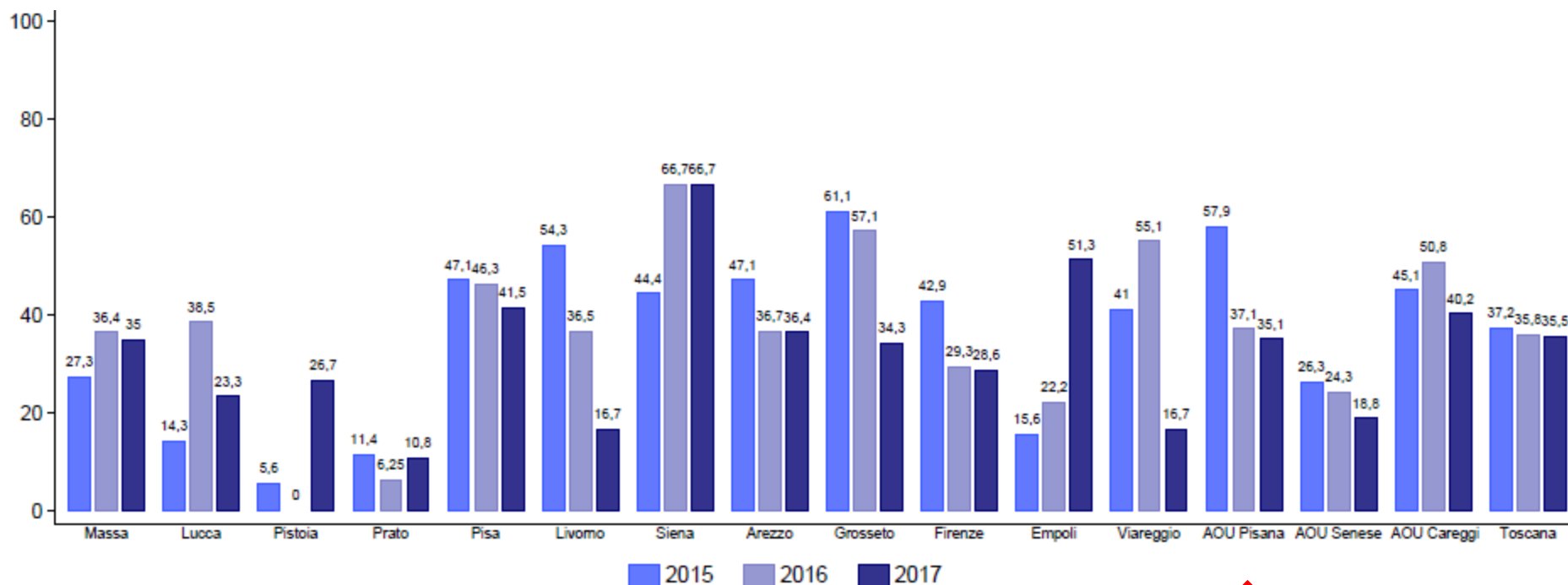
MORTALITY 30 DAYS



Multivariate logistic regression model regarding 30-day mortality

Variables	OR	95% CI OR	<i>p</i>
Age > 65 years	2.152	1.259 – 3.667	0.005
IDC	0.520	0.298 – 0.906	0.021

K. pneumoniae resistente a carbapenemi, Toscana, anni 2015-2017



Batteremie da CR-Kp

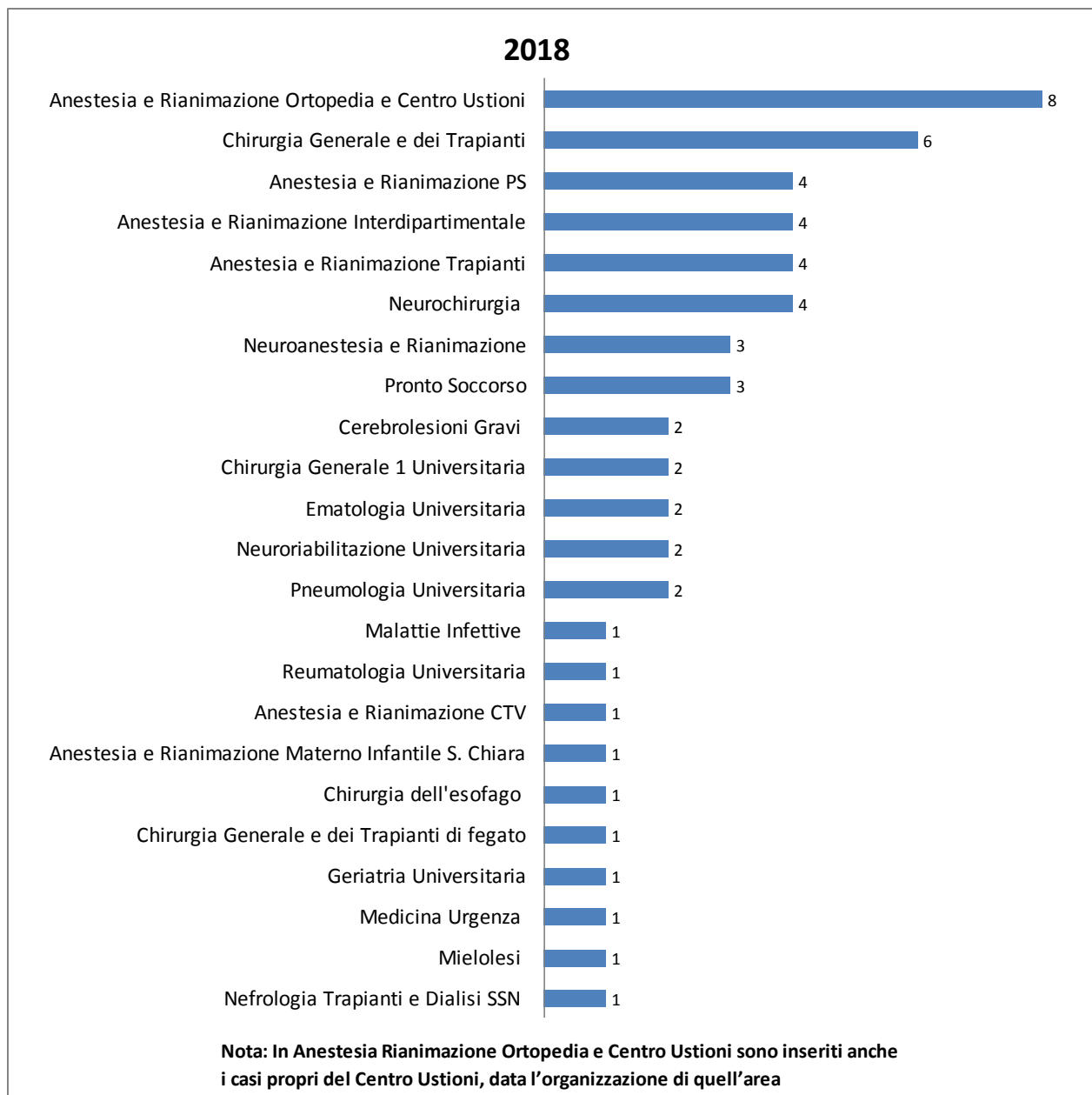
Anno	2014	2015	2016	2017	2018
Numero di pazienti	73	61	53	61	56
Incidenza/10.000 giornate di degenza	2,09	1,78	1,62	1,93	1,80

Colonizzazione e batteremie da CR-Kp

AOUP 2018

Area	N P.ti emo	% P.ti emo	N P.ti tot	% P.ti tot
Terapie Intensive	25	45%	134	33%
Reparti Chirurgici	14	25%	125	31%
Reparti Medici	9	16%	129	32%
Riabilitazioni	5	9%	14	3%
Pronto Soccorso	3	5%	3	1%
Totale	56	100%	405	100%

Batteriemie da K. pneumoniae resistente a Carbapenemi – Alert anno 2018



Setticemie da KPC-Kp

Variabili			
	2014	2015	2016
Casi	86	67	51
incidenza /1000 accessi	1,36	1,06	ND
incidenza /10000 gg deg	2,46	1,95	ND
Età media	66 ± 15	66 ± 14	64 ± 17
% M rispetto a F	62%	57%	67%
Reparti Medici	37%	33%	27%
Reparti Chirurgici	28%	31%	29%
Reparti UTI + C.ustioni	35%	36%	43%
% Pazienti in consulenza	41%	60%	45%
deg media	47 ± 38	47 ± 41	46 ± 39
deg media guariti	54 ± 34	53 ± 41	50 ± 34
Letalità 30 gg in consul	34%	28%	26%
Letalità 30 gg non consul	41%	48%	36%
Diff % dec 30 gg in cons	-7,2%	-20,6%	-9,6%
Esito letalità 30gg	38%	36%	31%
Letalità intraosp	50%	45%	37%

RAPID RISK ASSESSMENT

Regional outbreak of New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacteriaceae, Italy, 2018–2019

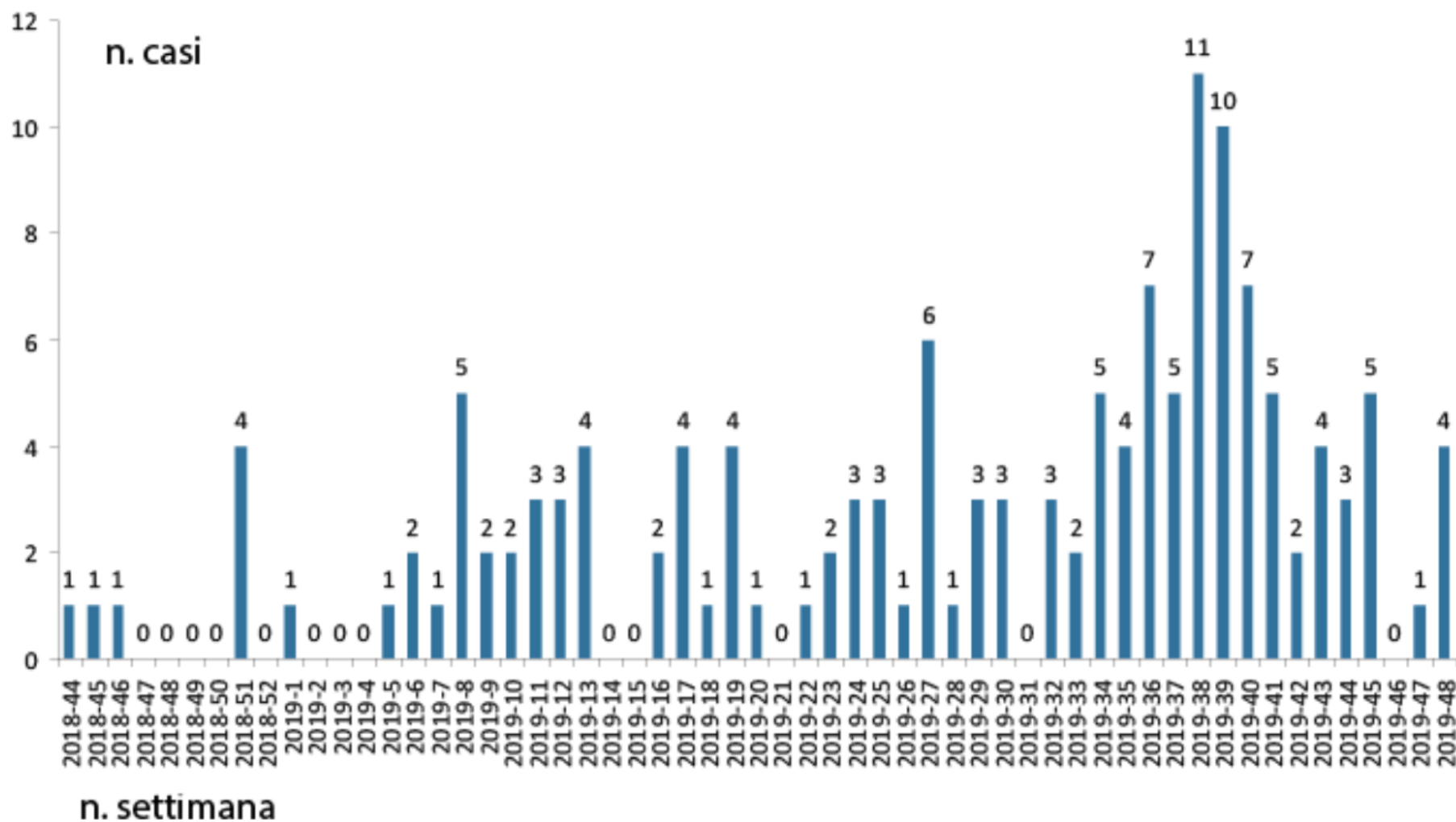
4 June 2019

NDM epidemic, Tuscany 2018-2019*

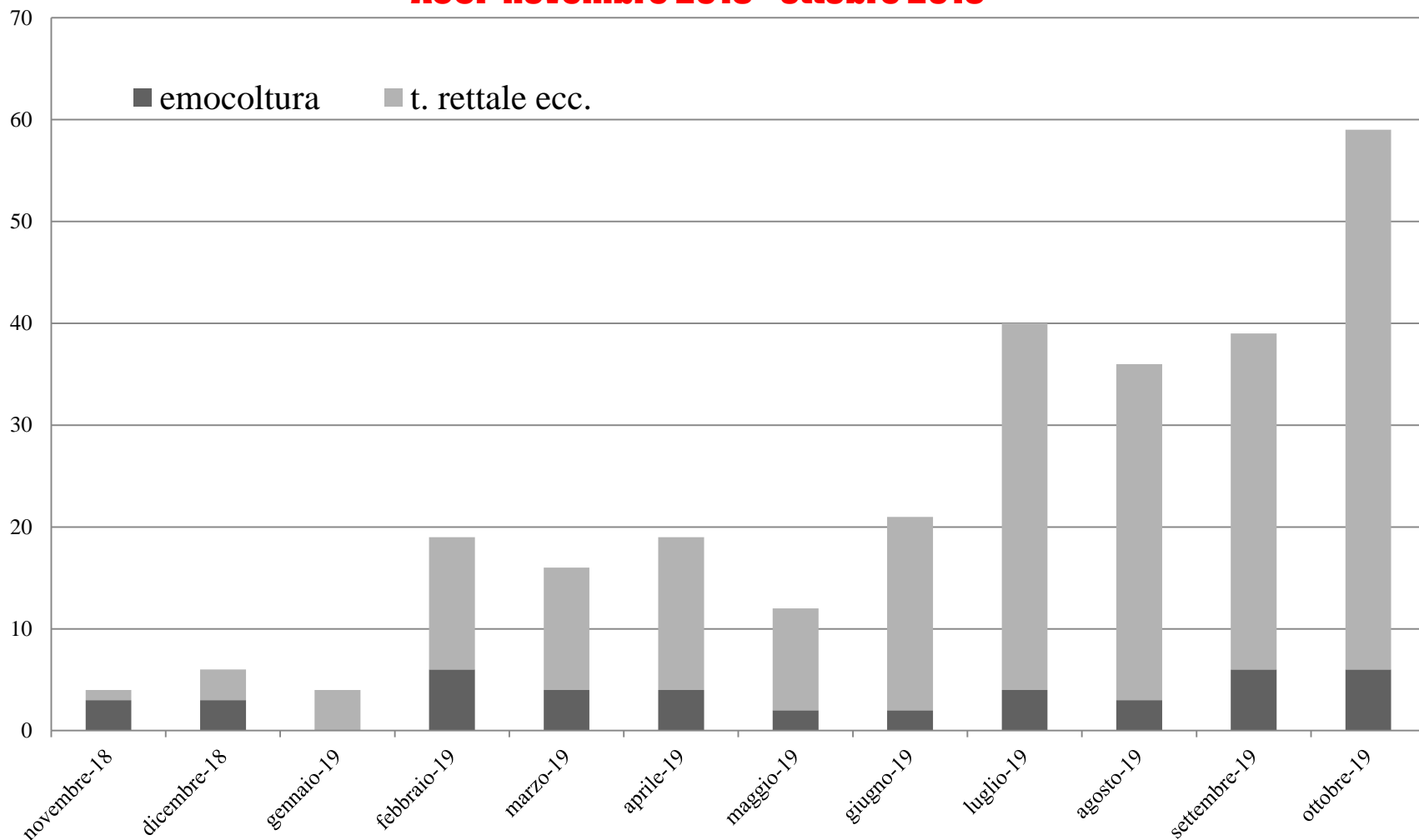
- Nov. 2018, mainly Tuscany North-West area
- Bacteremia 147 patients
- Deaths at 30 days: 48 patients
- Overall mortality: 33%
- Rectal Colonization: > 1500 (estimated)
- *K.pneumoniae* (clonal spread ST147), few *E.coli*
- Susceptible to: Aztreonam-Avibactam, Colistin (100%)
Fosfomycin, Tygecicline (80%)
- AZTREONAM+CEFTAZIDIME AVIBACTAM

* 11 Dicembre

Aggiornamento 11 dicembre 2019
da novembre 2018 batteri NDM sono stati isolati
nel sangue di 147 pazienti



Distribuzione NDM per materiale AOUN novembre 2018 - ottobre 2019



Antibiotic choice for MDR Enterobacteriaceae and non-fermenting GNB depending on genotype

	Enterobacteriaceae					<i>P. aeruginosa</i> (except for MBL)	<i>A. baumannii</i>
	ESBL	AmpC	KPC	OXA-48	IMP/VMP /NDM		
Piperacillin–tazobactam	Activity depending on MICs and/or target concentrations	Not active	Not active	Not active	Not active	Not active	Not active
Imipenem/meropenem	Active	Active	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Not active	Not active	Not active
Cefepime	Active	Active	Not active	Not active	Not active	Not active	Not active
Ceftazidime	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Not active	Not active	Not active	Not active	Not active
Aztreonam	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Active	Active	Not active
Colistin	Active	Active	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations
Tigecycline	Active	Active	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Not active	Activity depending on MICs and/or target concentrations
Aminoglycosides	Active	Active	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations	Activity depending on MICs and/or target concentrations



Active



Activity depending on MICs and/or target concentrations



Not active

Enterobacteriaceae

ESBL AmpC KPC MBL OXA-48

CEFT/TAZ

CAV/AVI

MER/VAB

IMI/REL

AZT/AVI

Eravacycline

Cefiderocol

Plazomicin



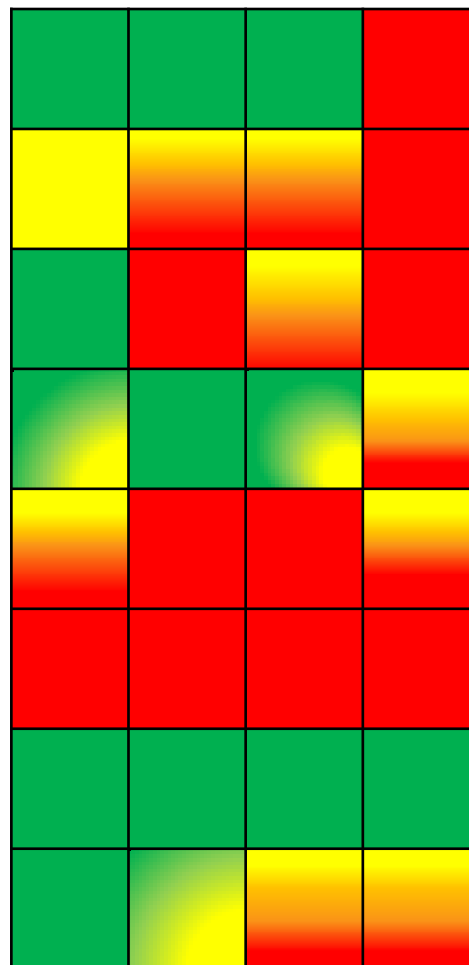
Active

Activity depending on MICs and/or target concentrations

Not active

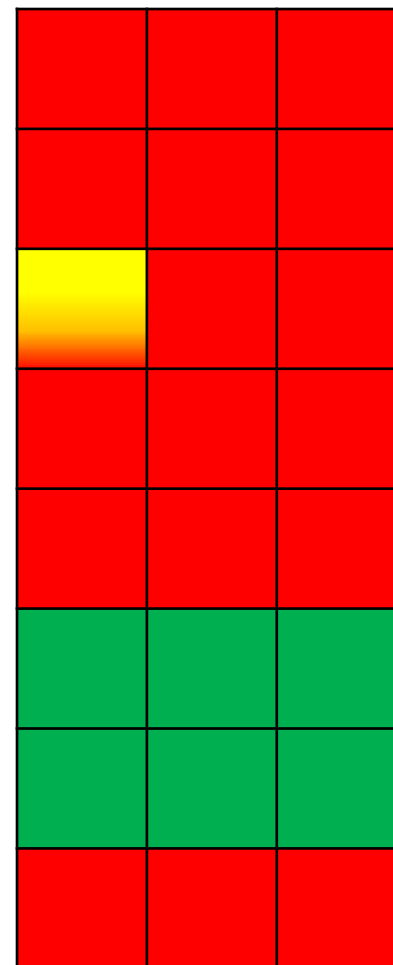
P. aeruginosa

AmpC Efflux Porin MBL



A. baumannii

OXA-23
OXA-40
AmpC OXA-50 MBL



Refertazione antibiogramma molecolare

ATB MOLECOLARE	SPECIE	REFERTO
KPC + NDM – VIM – OXA – CTX-M -	Enterobatteri	<i>Presenza di un gene per carbapenemasi tipo KPC: elevata probabilità di resistenza a tutti i betallatamici escluso CEFTAZIDIME/AVIBACTAM</i>
KPC – NDM + VIM – OXA – CTX-M -	Enterobatteri	<i>Presenza di un gene per carbapenemasi tipo NDM: elevata probabilità di resistenza a tutti i betallatamici escluso AZTREONAM (da associare ad avibactam)</i>

Gene-oriented antibiotic therapy for Enterobacterales



Molecular ATBG

CTX –
OXA 48 –
KPC –
NDM –
VIM –
IP –

Piperacillin/ta
zobactam

CTX +
OXA 48 –
KPC –
NDM –
VIM –
IP –

Meropenem
or
Ceftolozane/
tazobactam
3 g TID (*E. coli*)
o Ceftazidime/
avibactam (*K. Pneumoniae*)

CTX –
OXA 48 +
KPC –
NDM –
VIM –
IP –

Ceftazidime/
avibactam
or
Meropenem +/-
Tigecicyline +/-
Fosfomycin

CTX –
OXA 48 –
KPC +
NDM –
VIM –
IP –

Ceftazidime/
avibactam +
Fosfomycin
or
Colistin +/-
Tigecyline +/-
Fosfomycin

CTX –
OXA 48 –
KPC –
NDM +
VIM –
IP –

Aztreonam +
Ceftazidime/
avibactam
or
Colistin +
Fosfomycin +/-
Tigecycline

Conclusioni

- Investire in attività di Antimicrobial Stewardship è probabilmente vantaggioso per i pazienti e per il sistema
- Il lavoro di squadra, in particolare uno stretto rapporto con la Microbiologia, è fondamentale
- Interventi di *infection control* e di prevenzione risultano cruciali per ridurre le infezioni

AMR control require joining forces

