
# Enterobatteri ESBL positivi

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# Antimicrobici sistemici

# AIFA 2016

- **II° categoria farmaci in termini di spesa** ;
- 4,4 miliardi di euro / anno;
- **40 DDD x 1000 abitanti / die;**
- Spesa pro-capite 72,5 euro / anno ;
- **+ 9,5% Aumento spesa Antibiotici in Ospedale;**
- **74,2% Spesa Strutture Sanitarie Pubbliche;**
- 18,6% spesa : SSN in regime di convenzione;
- 7,2% spesa : privata del cittadino

# Antibioticoresistenza

- Abuso di antibiotici in campo umano
- **Uso inadeguato / inappropriato di antibiotici**
- Resistenze crociate
- Uso /Abuso di Antibiotici in campo veterinario
- Uso/Abuso di Antibiotici in agricoltura

# Obiettivo dei programmi di Antimicrobial Stewardship

- **Migliorare l' appropriatezza prescrittiva;**
- Ottimizzare il trattamento delle infezioni , in particolare di quelle gravi ;
- Minimizzare gli effetti collaterali;
- Prevenire l' insorgenza di resistenze

# Appropriatezza della terapia antibiotica

- Spettro antimicrobico idoneo;
- Timing d'inizio della terapia adeguato;
- Modalità di somministrazione ;
- Grado di esposizione all'antibiotico nella sede d'infezione ottimale ;
- Appropriatezza del dosaggio;
- Idonea frequenza di somministrazione;
- Monitoraggio delle concentrazioni plasmatiche;
- Durata limitata alla risoluzione clinica;

# Obiettivo dei programmi di Antimicrobial Stewardship

- Migliorare l' appropriatezza prescrittiva**;**
- **Ottimizzare il trattamento delle infezioni , in particolare di quelle gravi ;**
- Minimizzare gli effetti collaterali;
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## Criteri per ottimizzare terapia antibiotica delle infezioni gravi

- Fattori legati al paziente ;
- Fattori legati all'infezione;
- Fattori legati all' antibiotico ;
- Setting assistenziale

# Fattori legati al paziente

- **Presenza di fattori rischio**;
- Comorbosità;
- Presenza di allergie farmacologiche;
- Fisiopatologia dell’ ospite;
- Pregressi trattamenti antibiotici;
- Colonizzazione;
- Precedenti infezioni

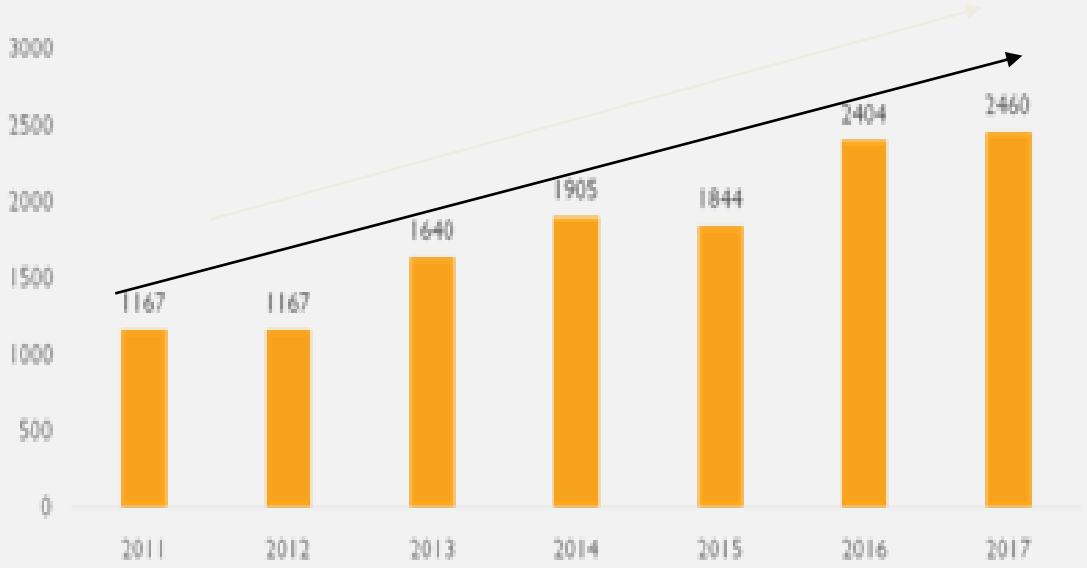
# Fattori legati all' infezione

- **Fattori di rischio per l'infezione;**
- Tipo d'infezione;
- Gravità della stessa;
- Sorgente dell'infezione (nella sepsi)
- Etiologia generale;
- **Patterns nazionali e/o locali di sensibilità**

# Fattori legati allo  antibiotico

- Spettro dell’ antibiotico: ampio, comprese le forme MDR;
- Attività battericida;
- Potenza elevata con evidenza di efficacia clinica;
- Profilo farmacocinetico (PK) /farmacodinamico (PD) favorevole;
- Scarsa induzione di resistenze;
- Manegevolezza: effetti indesiderati ed interazioni farmacologiche;

# CONSULENZE_INFETTIVOLOGICHE



# Fattori legati al paziente

- **Presenza di fattori rischio**;
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- Pregressi trattamenti antibiotici;
- Colonizzazione;
- Precedenti infezioni

# Selezione di patogeni resistenti legati all'abuso delle diverse classi di antibiotici

- **Cefalosporine di III generazione**
  - MRSA, MRSE
  - VRE
  - Streptococco pneumoniae PR
  - **Enterobacteriaceae ESBL +**
  - Enterobacteriaceae AmpC +
  - Acinetobacter MDR
  - Clostridium difficile

# Selezione di patogeni resistenti legati all'abuso delle diverse classi di antibiotici

- **Fluorchinolonici**
  - MRSA
  - Pseudomonas MDR
  - **Enterobacteriaceae ESBL +**
  - Enterobacteriaceae FR
  - Colite da Clostridium difficile

# ESBL : Fattori di rischio

- Età > 65 anni ;
- Comorbidità ;
- Allettamento;
- Demenza;
- Ospedalizzazione, RSA, Case di Riposo ecc.;
- **Impiego di cefalosporine III° generazione;**
- **Utilizzo di fluorchinoloni;**

# Fattori legati all' infezione

- **Fattori di rischio per l'infezione;**
- **Tipo d'infezione;**
- Gravità della stessa;
- Sorgente dell'infezione (nella sepsi)
- Etiologia generale;
- **Patterns nazionali e/o locali di sensibilità**

# MDRO
## **m**ulti-**d**rug **r**esistant **o**rganism

**PDR** = Pan Drug Resistance → resistenza a tutti i farmaci disponibili

**XDR** = Extensive Drug Resistance → resistenza a tutti i farmaci disponibili tranne 1o 2

**MDR** = Multi Drug Resistance → resistenza ad almeno 3 classi di antibiotici

# Perchè sono clinicamente importanti

Provocano  infezioni clinicamente sovrapponibili a quelle dalle stesse specie sensibili

Hanno opzioni terapeutiche estremamente  limitate
Sono associati con aumento dei giorni di  degenza, dei costi sanitari e della mortalità mortalità

# Epidemiologia delle infezioni da MDRO

Variabile per anno, area geografica, ospedale, reparto

Fondamentale conoscere i dati epidemiologici locali per predisporre un' appropriata terapia empirica

# Quali tra i Gram negativi ?

**Enterobatteri produttori di ESBL**

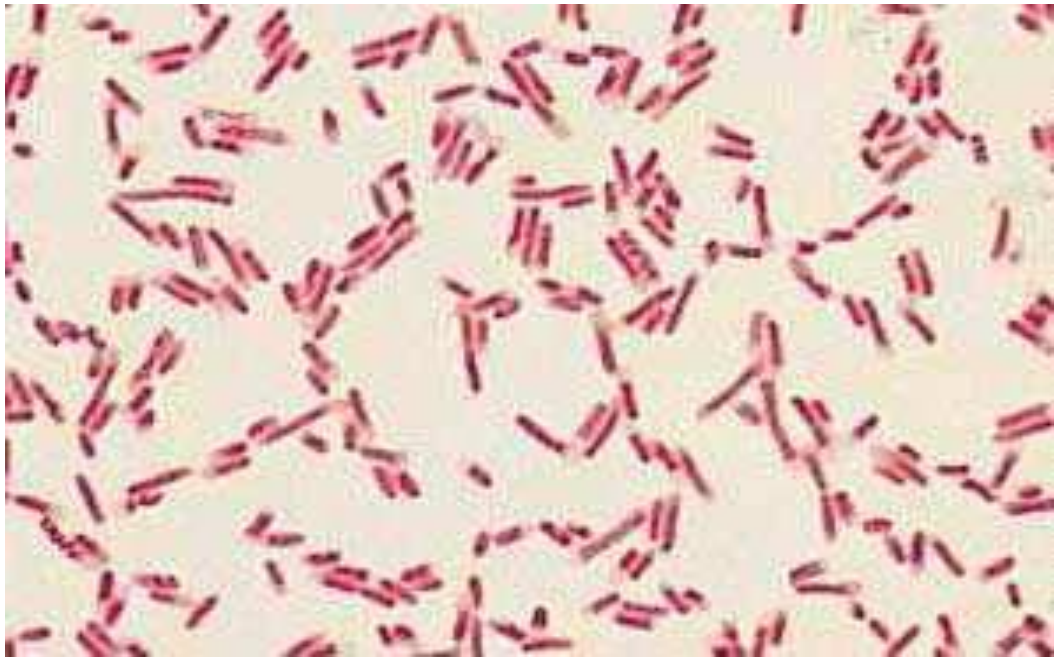
**Enterobatteri** resistenti ai carbapenemi

***Pseudomonas aeruginosa*** *multiresistente*

***Acinetobacter panresistenti***

# Batteri gram negativi produttori di Beta Lattamasi a Spettro Esteso

# ESBL



***Enterobatteri***

***E.coli, Klebsiella, Enterobacter, Serratia, Citrobacter***
***Proteus, Salmonella, Shigella, Yersinia***

# ESBL

- Enzimi in grado di inibire le cefalosporine di III generazione,
- Comparsa: 1983.
- Si conoscono >200 ESBL.
- Codificate da geni plasmidici, derivati da mutazioni di TEM-1 e TEM-2, CTX-M, OXA.
- Prodotte prevalentemente da *Eschericia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*

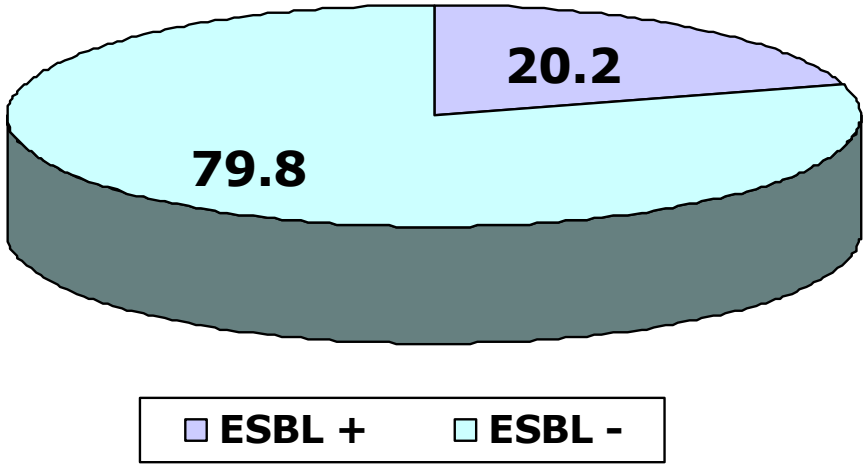
Conferiscono **resistenza** a penicilline, cefalosporine, aztreonam.
**Non conferiscono resistenza** a cefamicine e carbapenemici.

# ESBL

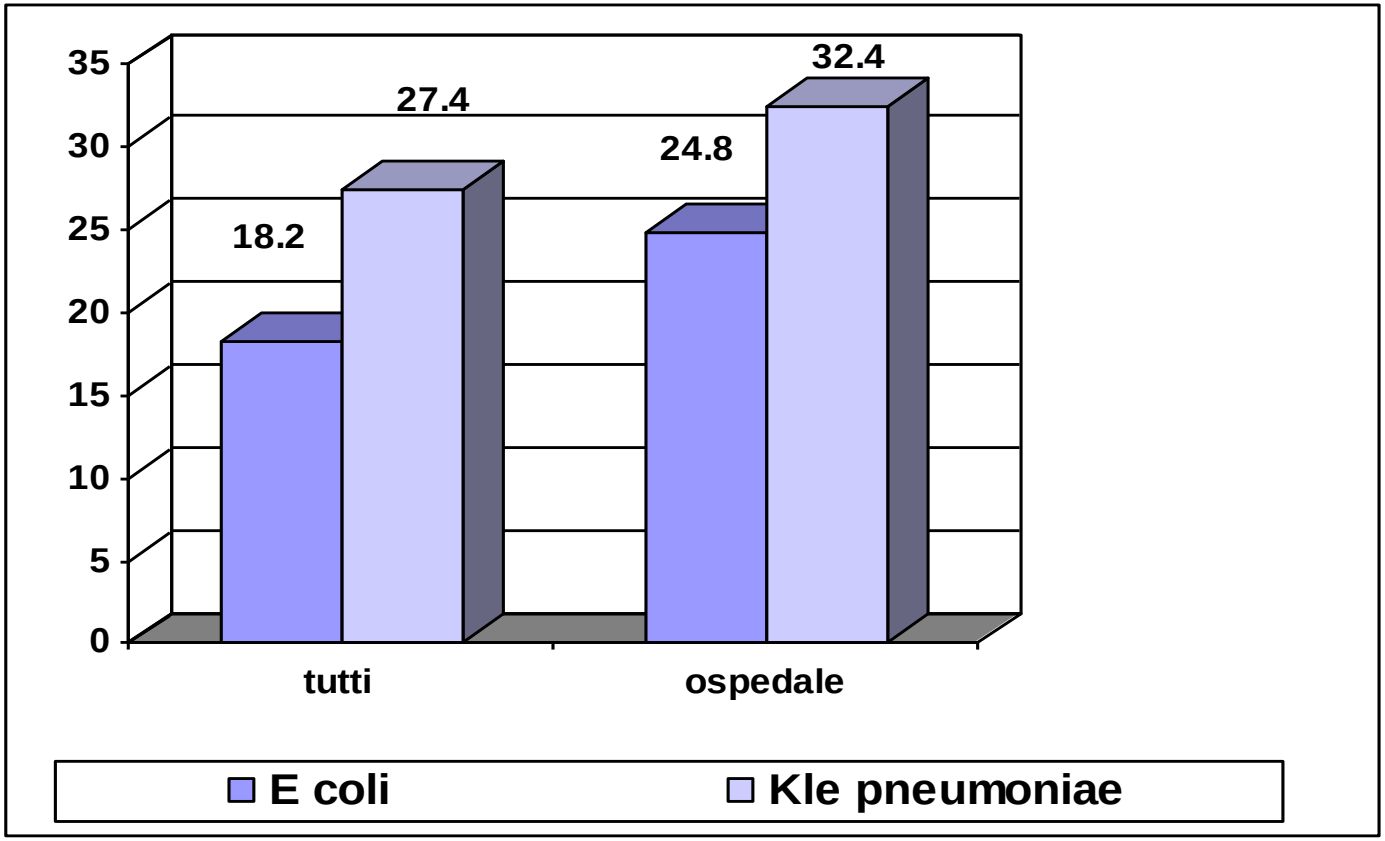
Alcune ESBL (**CTX-M**), oltre a conferire la multiresistenza ai betalattamici, sono anche in grado di indurre una resistenza ad antibiotici quali **chinoloni, aminoglicosidi e trimethoprim** che non appartengono alla famiglia dei β-lattamici.

# E.coli, Klebsiella produttori di ESBL FERRARA 2017

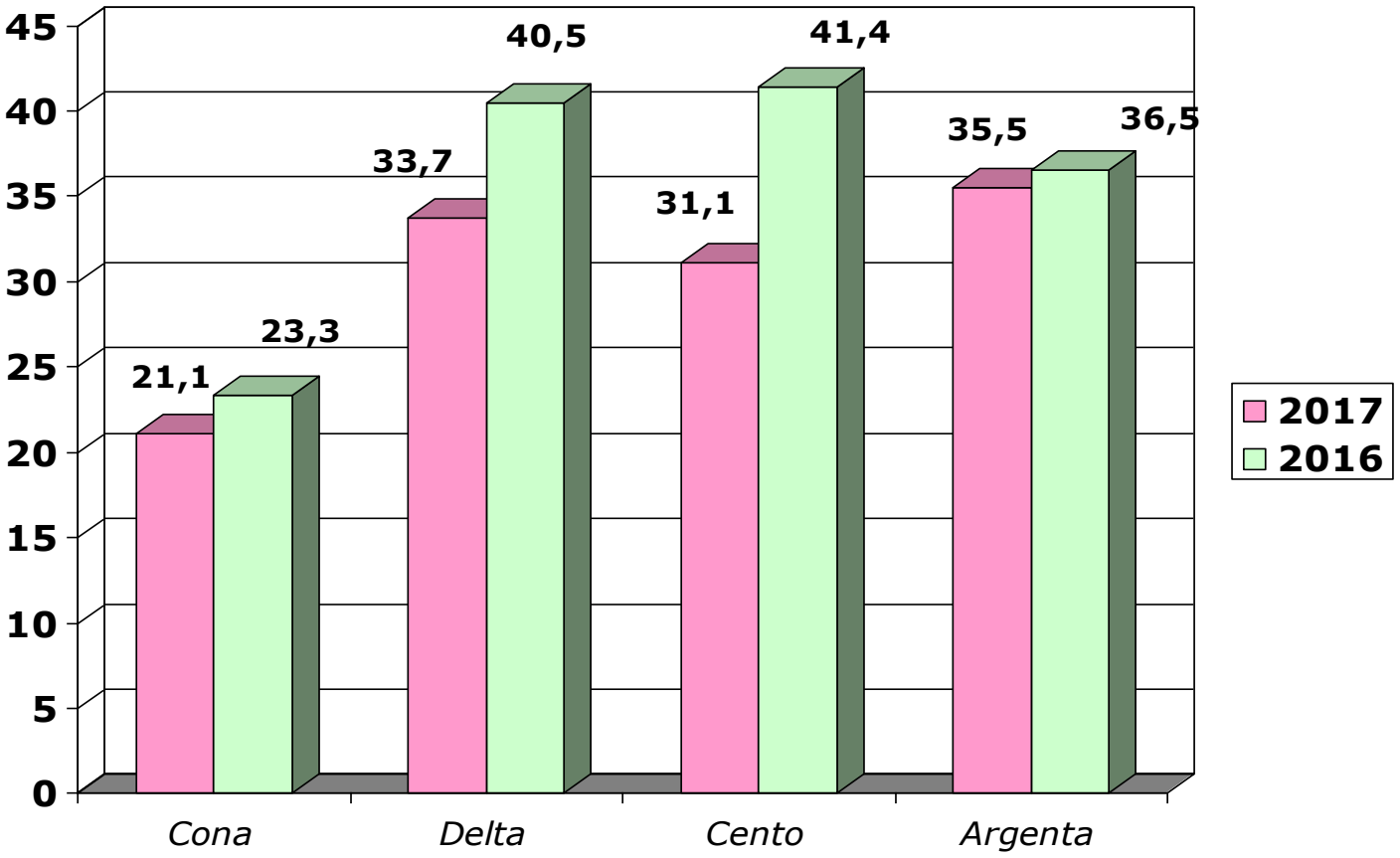
**Totali 5271**
**ESBL 1066 (20,2 %)**



# % di E.coli e Klebsiella produttori di ESBL Ferrara 2017



# E. coli ESBL % 2016-2017



# K. pneumoniae % ESBL

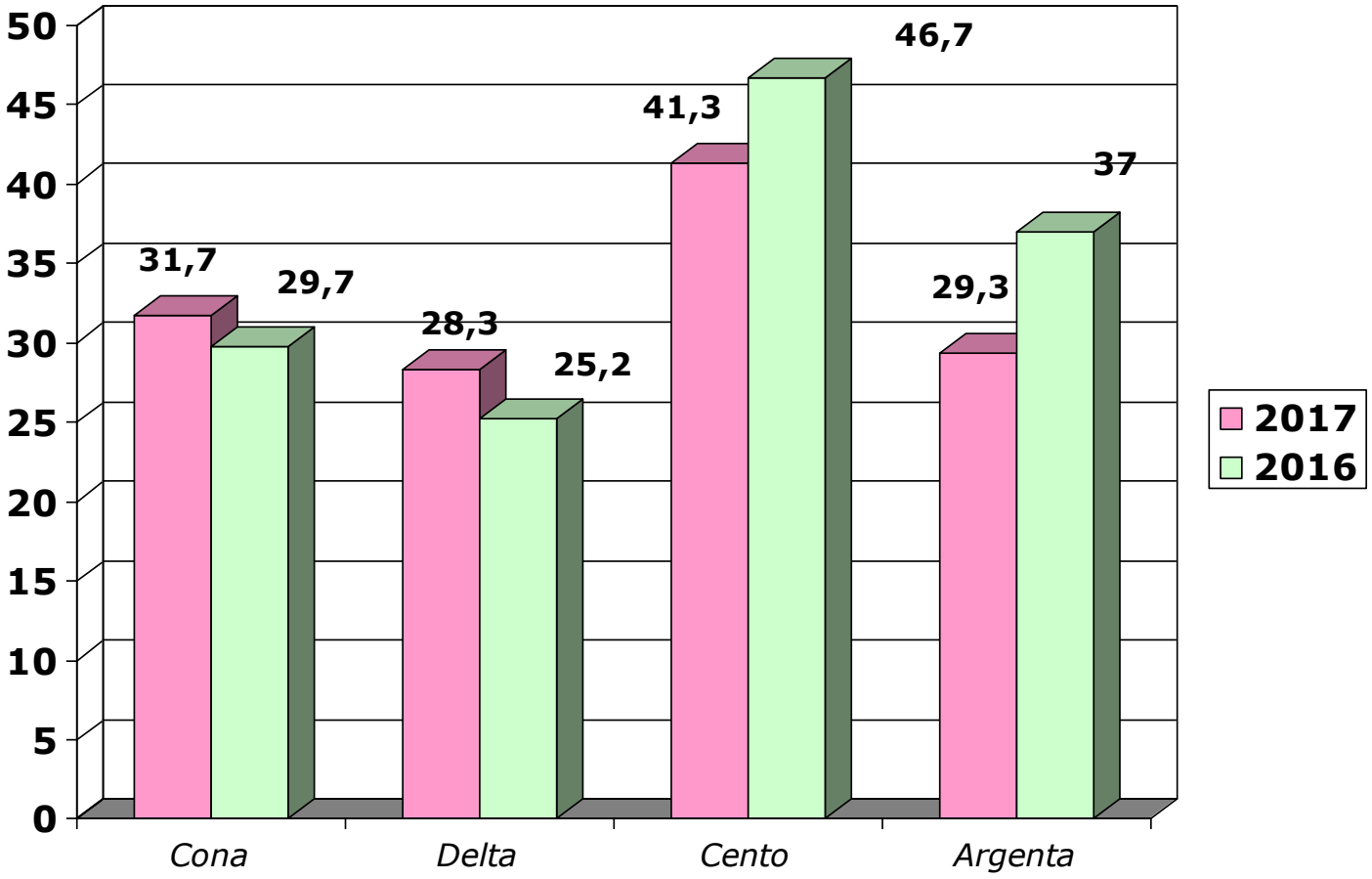
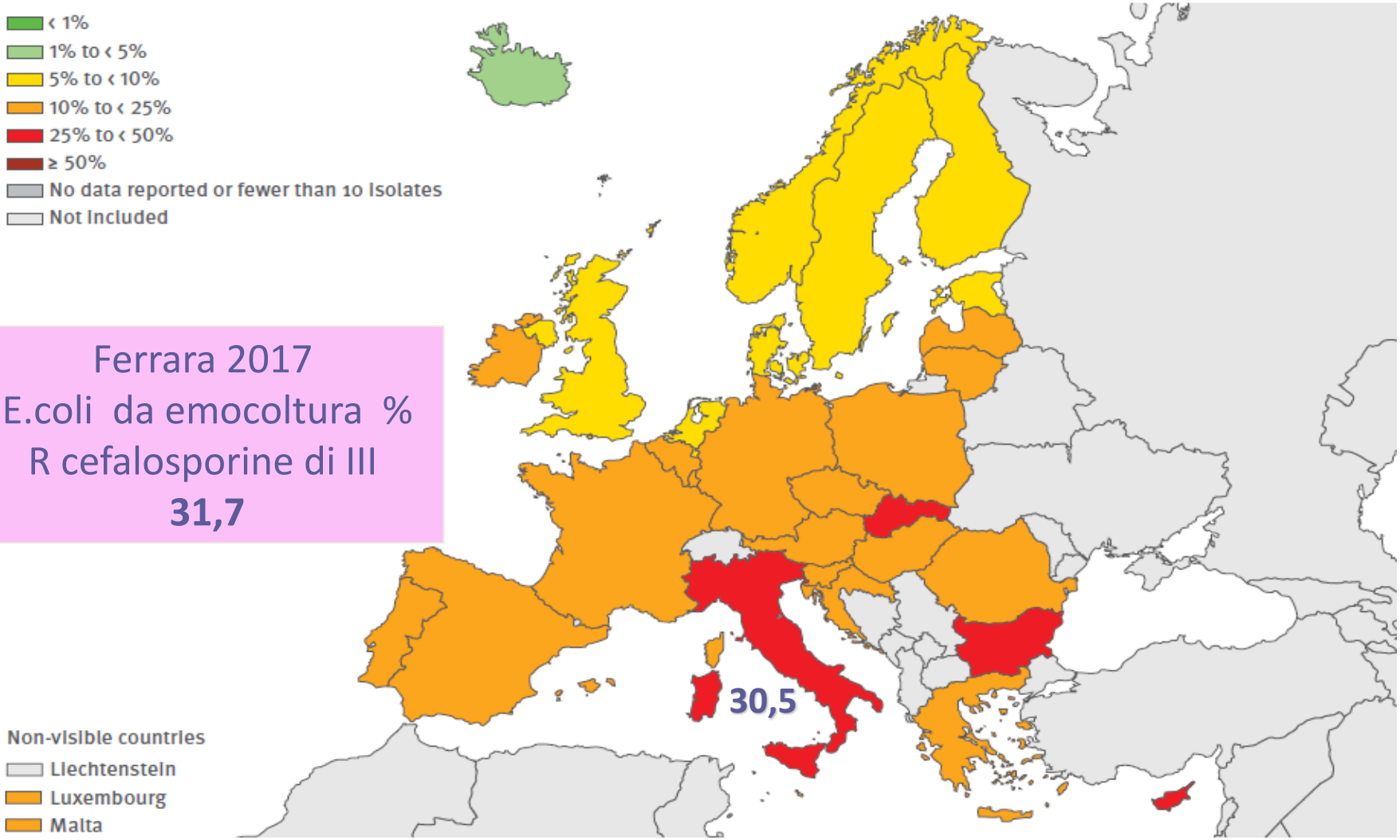


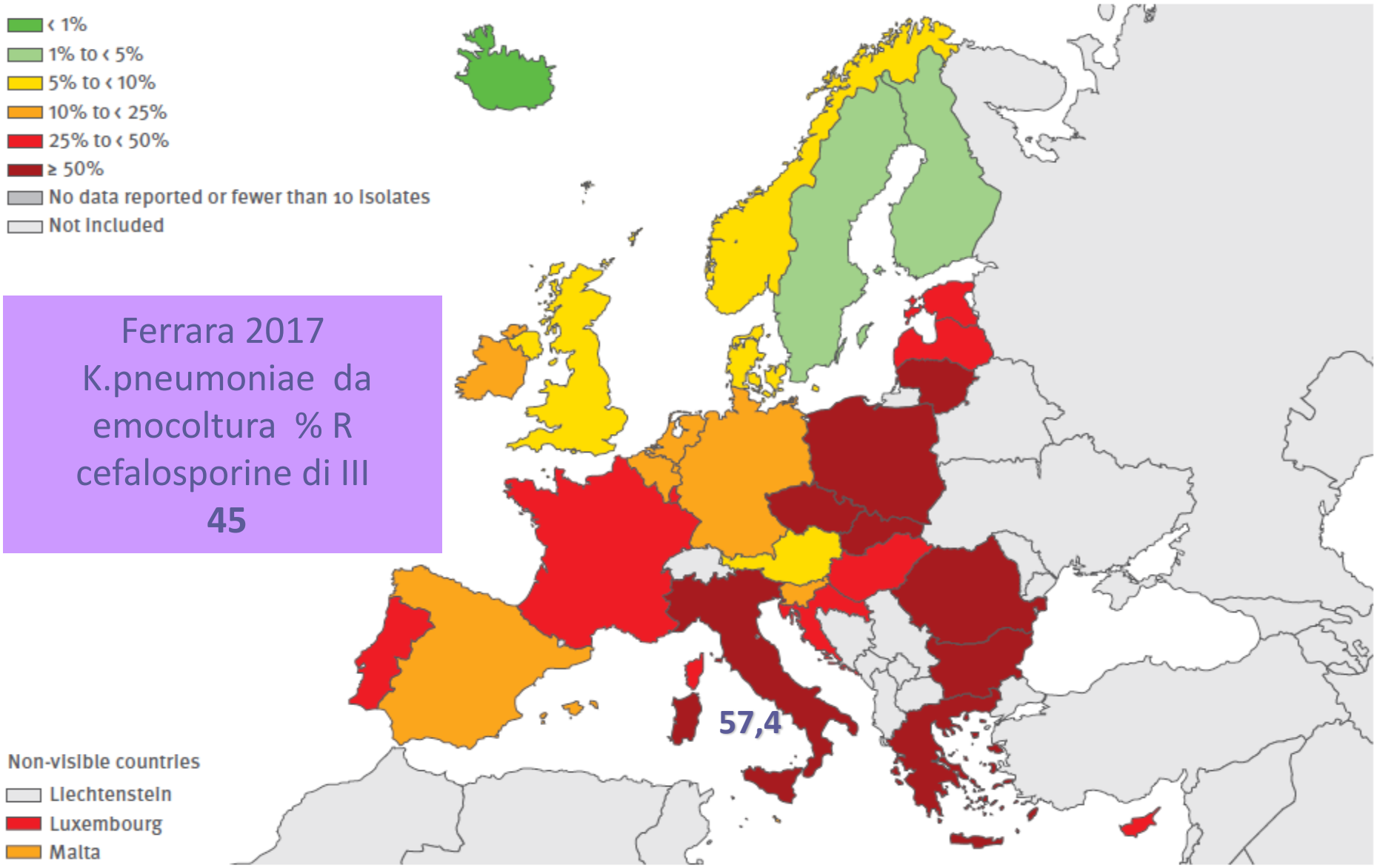
Figure 3.3. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2016




Ferrara 2017
E.coli da emocoltura %
R cefalosporine di III
**31,7**

**E1**. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2016. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017. Publication pending, November 2017

cephalosporins, by country, EU/EEA countries, 2016



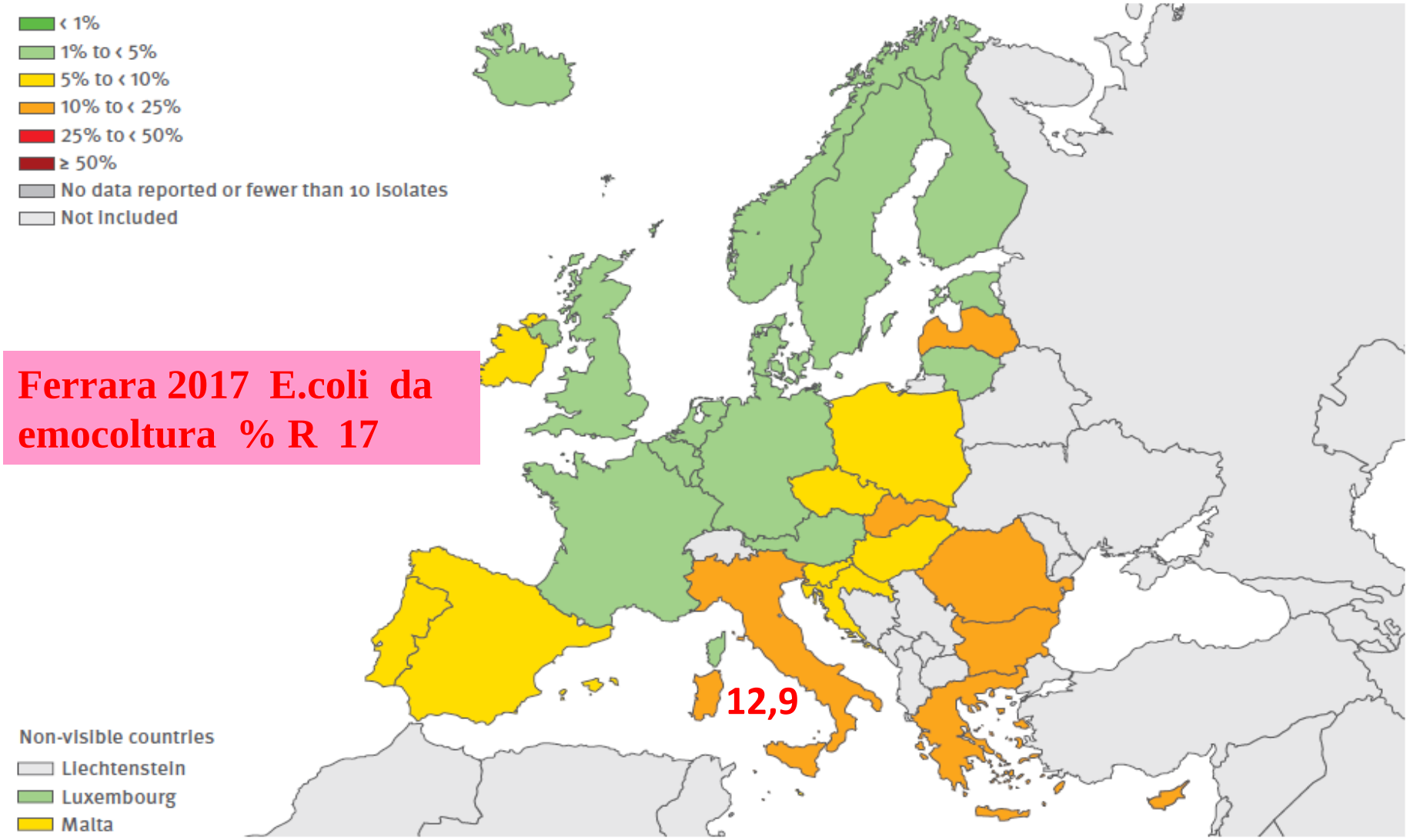

Ferrara 2017
K.pneumoniae da emocoltura % R cefalosporine di III
**45**

**E1**. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2016. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017. Publication pending, November 2017

# ESBL

Alcune ESBL (**CTX-M**), oltre a conferire la multiresistenza ai betalattamici, sono anche in grado di indurre una resistenza ad antibiotici quali **chinoloni, aminoglicosidi e trimethoprim** che non appartengono alla famiglia dei β-lattamici.

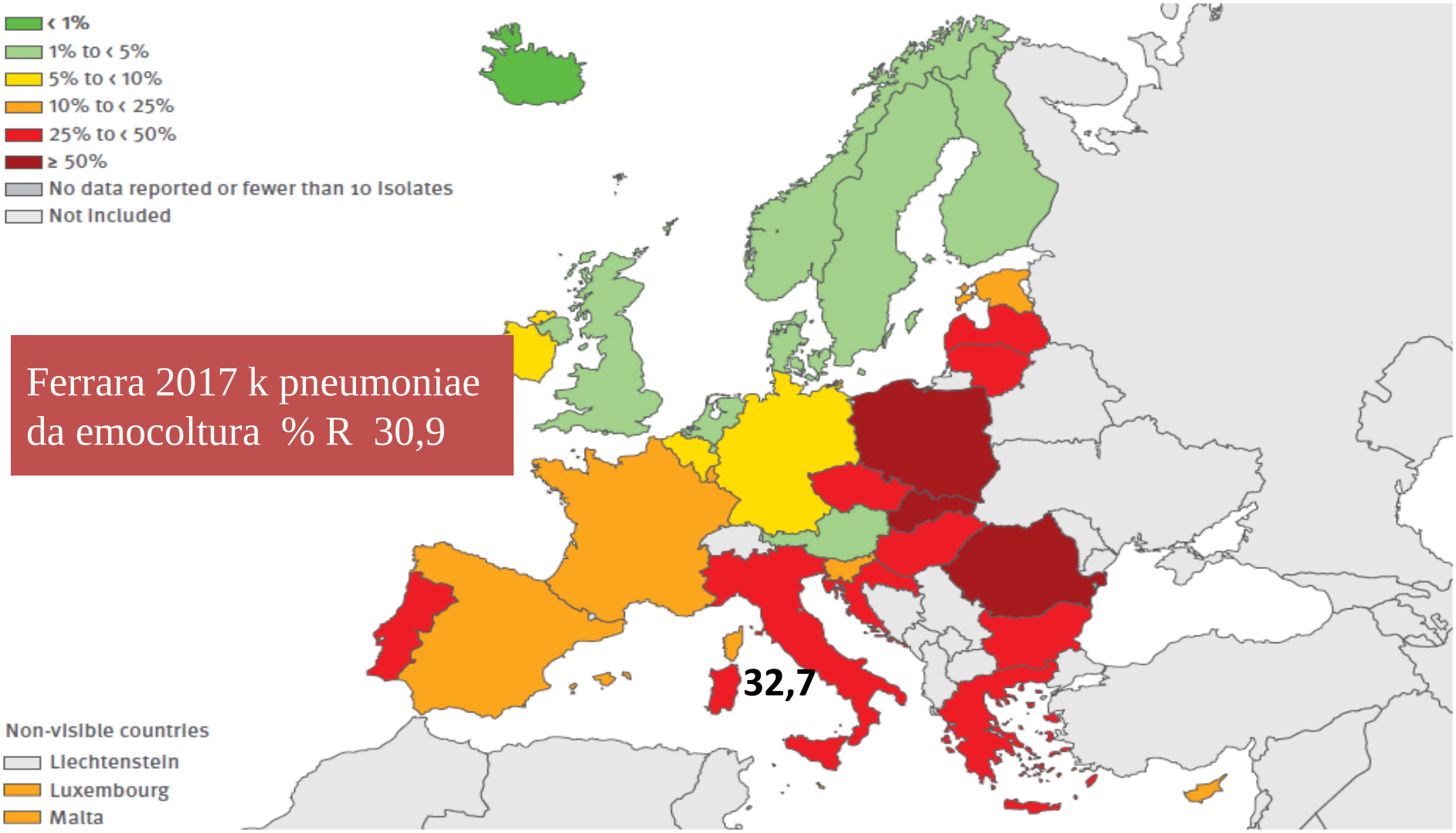
Figure 3.6. *Escherichia coli*. Percentage (%) of invasive isolates with combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, by country, EU/EEA countries, 2016




**Ferrara 2017 E.coli da emocoltura % R 17**

**E1**. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2016. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017. Publication pending, November 2017

Figure 3.12. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with combined resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides, by country, EU/EEA countries, 2016




**E1**. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2016. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017. Publication pending, November 2017

# Infezioni da enterobatteri ESBL

- Batteriemie/sepsi ;
- Infezioni urinarie complicate e non ;
- Infezioni endoaddominali ;
- CAP ;
- Polmoniti correlate alle cure sanitarie ;
- Infezioni ginecologiche;

# Interrompere il circolo vizioso

**Infezioni da Enterobacteriaceae**

Fluorchinoloni o Cefalosporine III° generazione

**Enterobatteri ESBL +**

Carbapenemi

CPE , Metallo B- lattamasi , Candidemia ecc.

Politiche e Strategie terapeutiche per limitare Cefalosp. III° e Fluorchinoloni

Piperacillina/Tazobactam +/- Amikacina

oppure

Ceftolozano/Tazobactam

# Indirizzi di Politica degli Antibiotici
# Nel 2013 : 24 DDD/100 gg degenza > 2016 : 11 DDD/100 gg degenza


**RIDUZIONE DELLA PRESCRIZIONE DI FLUORCHINOLONICI SISTEMICI IN UNA GRANDE AZIENDA OSPEDALIERA UNIVERSITARIA DEL NORD – ITALIA, DOPO APPLICAZIONI STRATEGICHE DI POLITICA DEGLI ANTIBIOTICI**

Libanore M, Carletti R, Antonelli T, Antonioli PM, Rossi R, Cultrera, Pantaleoni M, Cazzorla C, Gallerani M, Scanavacca P

Gruppo per l' Uso Responsabile degli Antibiotici e per il Controllo e la Sorveglianza delle Infezioni correlate all' assistenza sanitaria, Azienda Ospedaliera Universitaria di Ferrara.

# Azienda Ospedaliera Universitaria Ferrara - Indicatori

| **Anno** | Antibiotici Totali x 100 gg degenza | Fluorchinoloni x 100 gg degenza | **Carbapenemi x 100 gg degenza** | Glicopeptidi: Vanco > 60% Versus Altri anti-MRSA |
|---|---|---|---|---|
| 2016 | 99,8 | **11,4** | 4,5 | N.R. |
| 2017 | 84,9 | **7,6** | 3,8 | + 4%<br>Solo Dip. Chirurgico<br>Gli altri virtuosi |


# UN PROGETTO PILOTA DI ANTIMICROBIAL STEWARDSHIP TERRITORIALE IN EMILIA ORIENTALE

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Unità Operativa Complessa Malattie Infettive, Azienda Ospedaliera – Universitaria Ferrara; * Istituto Malattie Infettive, Università degli Studi Ferrara ; * Servizio di Igiene Ospedaliera, Direzione Medica, Azienda Ospedaliera Universitaria Ferrara; * * Sezione di Microbiologia Clinica, Laboratorio Unico Provinciale, Azienda Ospedaliera – Universitaria Ferrara; * * * Unità Operativa Complessa Farmacia Ospedaliera, Azienda Ospedaliera Universitaria Ferrara; *** Unità Operativa Complessa Cure Primarie, Azienda USL Ferrara; * * * * Direzione Sanitaria Azienda USL Ferrara; **** Unità Operativa Complessa Farmacia, Azienda USL Ferrara; ***** Medici di Medicina Generale, * * * * * Valeocon Management Consulting Milano

**PREMESSE:** l' inappropriatezza prescrittiva degli antibiotici incrementa il livello di resistenza della flora microbica circolante nel territorio. Questo si traduce in un aumento delle infezioni da patogeni difficili e degli insuccessi terapeutici, con un forte impatto sulla spesa sanitaria.

**OBIETTIVO DEL PROGETTO:** ampliare le conoscenze dei Medici di Medicina Generale (MMG) per favorire il processo di appropriatezza prescrittiva e l' ottimizzazione delle risorse; aggiornare periodicamente sui cambiamenti dei profili di resistenza della flora batterica territoriale, al fine di adeguare la terapia antibiotica delle principali infezioni ad elevato impatto epidemiologico: infezioni delle basse vie respiratorie ed infezioni delle vie urinarie ; realizzare una gestione strutturata della terapia antibiotica, che tenga conto della realtà locale, in modo da ridurre i consumi impropri di antibiotici; definizione di un processo di comunicazione ed analisi tra territorio ed Azienda Ospedaliera Universitaria. (Figura 1).

**RISULTATI:** Un team di professionisti con elevata competenza in ambito di terapia antibiotica, coadiuvati da una agenzia di consulenza di management e una rappresentanza significativa dei MMG, dopo aver analizzato la letteratura internazionale sull' argomento, i dati epidemiologici riguardanti gli aspetti microbiologici e gli orientamenti prescrittivi dei sanitari del nostro territorio, hanno elaborato due algoritmi diagnostico terapeutici finalizzati alla gestione appropriata delle infezioni delle basse vie respiratorie e di quelle urinarie ( Algoritmo 1 e 2). Il progetto è stato presentato in seduta plenaria e condiviso con tutti i MMG dell' Emilia Orientale ( 253 sanitari).

**CONCLUSIONI:** correzione dei comportamenti errati dei MMG; riduzione dei ricoveri per infezioni delle vie urinarie e delle basse vie respiratorie; diminuzione dei costi di sistema: antibiotici e costi diretti ed indiretti legati ai ricoveri ospedalieri. Diminuzione dell' impiego di fluorchinoloni e cefalosporine di III° generazione, limitazione del ricorso all' urinocoltura, in particolare per le persone di sesso femminile, dei ricoveri dopo applicazione degli algoritmi (durata 6 mesi) confrontato con un periodo di durata analogo, precedente l' adozione delle flow- charts sopra indicate.

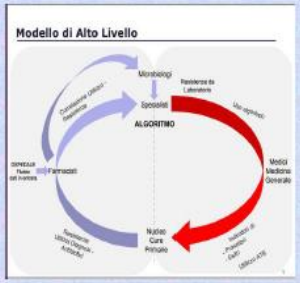
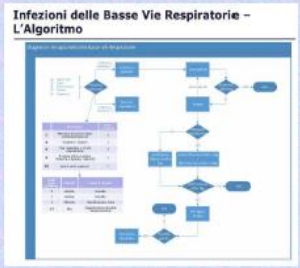


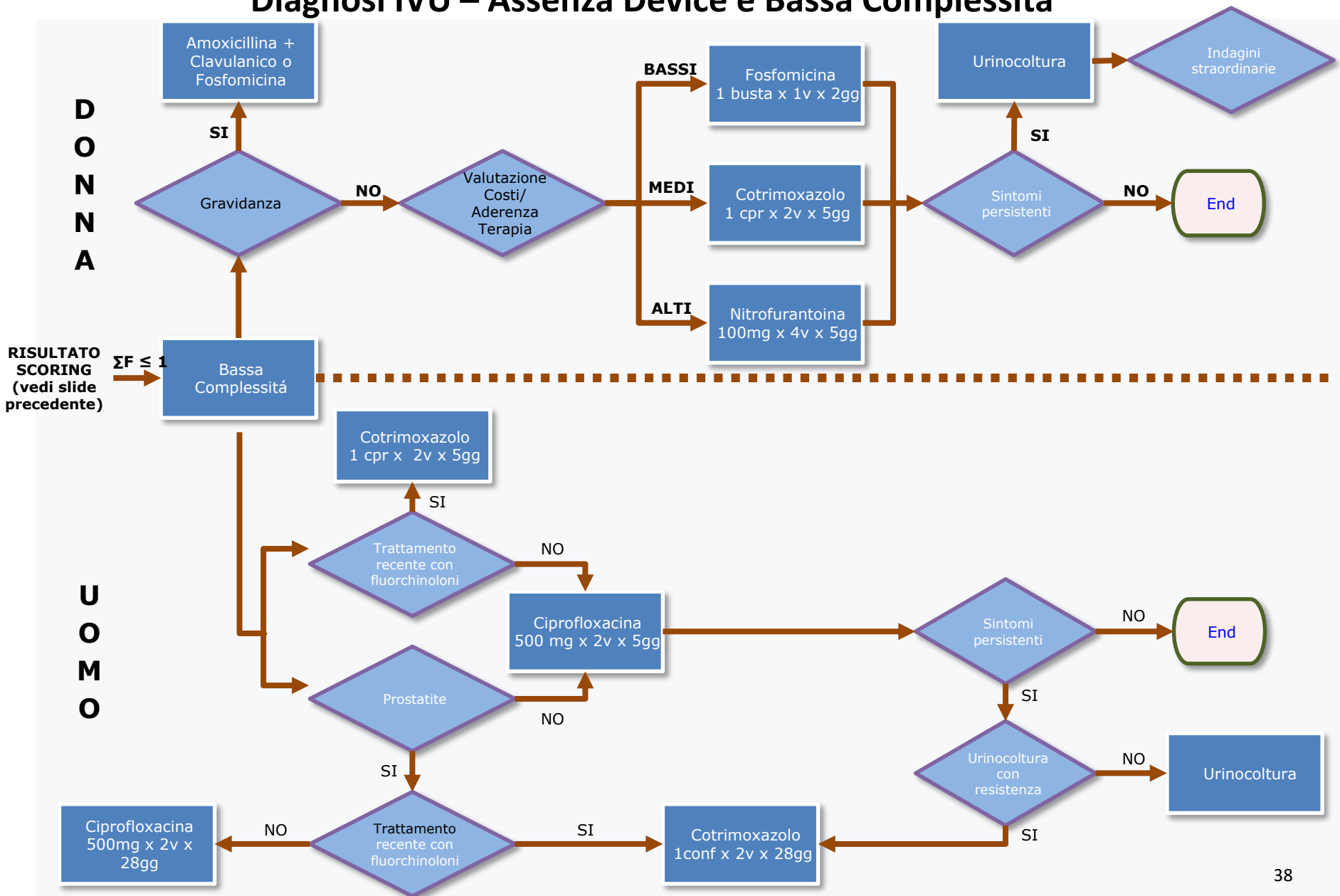

Figura 1. Modello di alto livello. .




Algoritmo 1. Infezioni delle Basse Vie Respiratorie.


Algoritmo 2. Infezioni delle Vie Urinarie.

# Diagnosi IVU – Assenza Device e Bassa Complessitá



# Infezioni da enterobatteri ESBL

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- CAP ;
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Sartelli et al. World Journal of Emergency Surgery (2017) 12:29
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World Journal of Emergency Surgery

REVIEW Open Access

# The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections

Massimo Sartelli[1*], Alain Chichom-Mefire[2], Francesco M. Labricciosa[3], Timothy Hardcastle[4], Fikri M. Abu-Zidan[5], Abdulrashid K. Adesunkanmi[6], Luca Ansaloni[7], Miklosh Bala[8], Zsolt J. Balogh[9], Marcelo A. Beltrán[10], Offir Ben-Ishay[11], Walter L. Biffl[12], Arianna Birindelli[13], Miguel A. Cainzos[14], Gianbattista Catalini[1], Marco Ceresoli[7], Asri Che Jusoh[15], Osvaldo Chiara[16], Federico Coccolini[7], Raul Coimbra[17], Francesco Cortese[18], Zaza Demetrashvili[19], Salomone Di Saverio[13], Jose J. Diaz[20], Valery N. Egiev[21], Paula Ferrada[22], Gustavo P. Fraga[23], Wagih M. Ghnnam[24], Jae Gil Lee[25], Carlos A. Gomes[26], Andreas Hecker[27], Torsten Herzog[28], Jae Il Kim[29], Kenji Inaba[30], Arda Isik[31], Aleksandar Karamarkovic[32], Jeffry Kashuk[33], Vladimir Khokha[34], Andrew W. Kirkpatrick[35], Yoram Kluger[36], Kaoru Koike[37], Victor Y. Kong[38], Ari Leppaniemi[39], Gustavo M. Machain[40], Ronald V. Maier[41], Sanjay Marwah[42], Michael E. McFarlane[43], Giulia Montori[7], Ernest E. Moore[44], Ionut Negoi[45], Iyiade Olaoye[46], Abdelkarim H. Omari[47], Carlos A. Ordonez[48], Bruno M. Pereira[23], Gerson A. Pereira Júnior[49], Guntars Pupelis[50], Tarcisio Reis[51], Boris Sakakhushev[52], Norio Sato[53], Helmut A. Segovia Lohse[40], Vishal G. Shelat[54], Kjetil Søreide[55,64], Waldemar Uhl[28], Jan Ulrych[56], Harry Van Goor[57], George C. Velmahos[58], Kuo-Ching Yuan[59], Imtiaz Wani[60], Dieter G. Weber[61], Sanoop K. Zachariah[62] and Fausto Catena[63]

# Tipo d'infezione endoaaddominale

**Table 3** Source of infection in 4553 patients from 132 hospitals worldwide (15 October 2014–2015 February 2015) [1]

| Source of infection | Number (%) |
|---|---|
| Appendicitis | 1553 (34.2) |
| Cholecystitis | 837 (18.5) |
| Post-operative | 387 (8.5) |
| Colonic non-diverticular perforation | 269 (5.9) |
| Gastro-duodenal perforations | 498 (11) |
| Diverticulitis | 234 (5.2) |
| Small bowel perforation | 243 (5.4) |
| Others | 348 (7.7) |
| PID | 50 (1.1) |
| Post traumatic perforation | 114 (2.5) |
| Total | 4553 (100) |

# Fattori legati allo  antibiotico

- Spettro dell’ antibiotico: ampio, comprese le forme MDR;
- Attività battericida;
- Potenza elevata con evidenza di efficacia clinica;
- Profilo farmacocinetico (PK) /farmacodinamico (PD) favorevole;
- Scarsa induzione di resistenze;
- Manegevolezza: effetti indesiderati ed interazioni farmacologiche;

# Opzioni terapeutiche a disposizione

- **Piperacillina- Tazobactam**;
- Tigeciclina;
- Ertapenem ;
- **Ceftolozano-Tazobactam;**
- **Meropenem;**
- Ceftazidime/Avibactam

# Tigeciclina

- Batteriostatico ;
- Non attivo su Proteus, Pseudomonas aeruginosa;
- Approvato per Infezioni endoaddominali , cute e tessuti molli;
- Non garanzie in monoterapia nel paziente settico;

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# Is It Time to Rethink the Notion of Carbapenem-Sparing Therapy Against Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* Bloodstream Infections? A Critical Review

Daniel B. Chastain, PharmD, AAHIVP[1],
Bryan P. White, PharmD[2], David A. Cretella, PharmD[3],
and Christopher M. Bland, PharmD, FCCP, FIDSA, BCPS[4]

**Table 1.** Study Data Comparing the Treatment of Extended-Spectrum β-Lactamase Bloodstream Infections with BL/BLIs versus Carbapenems.[9,10,17-21]

| Study | Empirical or Definitive | Number of Participants (BL/BLI vs Carbapenem) | Percentage Urinary Source or Biliary Tract (BL/BLI vs Carbapenem) | Percentage ICU (BL/BLI vs Carbapenem) | Percentage *Escherichia coli* | Mortality End Point (BL/BLI vs Carbapenem) |
|---|---|---|---|---|---|---|
| Rodríguez-Baño et al[9] (2012) | Empirical (n = 103) | 72 vs 31 | 72.2% vs 58.1% | 9.9% vs 6.7% | 100% | 9.7% vs 19.4% ($P > 0.20$)[a] |
| Rodríguez-Baño et al[9] (2012) | Definitive (n = 174) | 54 vs 120 | 77.8% vs 65.8% | 7.4% vs 15.4% | 100% | 9.3% vs 16.7% ($P > 0.20$) [a] |
| Kang et al[10] (2012) | Empirical (n = 114) | 36 vs 78 | Not reported | Not reported | 68.4% | 22.2% vs 26.9% ($P = 0.592$)[a] |
| Ofer-Friedman et al[17] (2015) | Mixed (n = 79)[b] | 10 vs 69 | 17% | Not reported | 53% | 60% vs 34% ($P = 0.10$)[a]; 80% vs 48% (OR = 4.5; 95% CI = 1.01 to 34; $P = 0.05$)[c] |
| Tamma et al[18] (2015) | Empirical (n = 213) | 103 vs 110 | 26.2% vs 30.3 % | 32.0% vs 35.5% | 31% | 1.92 (95% CI = 1.07-3.45; $P = 0.03$)[d] |
| Ng et al[19] (2016) | Empirical (n = 151) | 94 vs 57 | 63.8% vs 75.5% | 5.3% vs 14.0% | 66.9% | 30.9% vs 29.8% ($P = 0.89$)[a] |
| Gutiérrez-Gutiérrez et al[20] (2016) | Empirical (n = 365) | 170 vs 195 | 60% vs 59% | 7.6% vs 13.3% | 72.3% | 17.6% vs 20% (95% CI = −10.2% to 5.8%; $P = 0.6$)[a] |
| Gutiérrez-Gutiérrez et al[20] (2016) | Definitive (n = 601) | 92 vs 509 | 52.2% vs 58% | 4.3% vs 12.2% | 73.0% | 13.9% vs 9.8% (95% CI = −10.2% to 5.8%; $P = 0.28$)[a] |
| Gudiol et al[21] (2017) | Empirical (n = 174) | 48 vs 126 | 6.9% Each | 14.5% vs 23.8% | 73.6% | 20.8% vs 13.4% ($P = 0.33$)[a] |
| Gudiol et al[21] (2017) | Definitive (n = 251) | 17 vs 232 | 6.9% Each | 11.7% vs 18.8% | 74.9% | 5.8% vs 15.8% ($P = 0.99$)[a] |

Abbreviations: BL, β-lactam; BLI, β-lactamase inhibitors; ICU, intensive care unit; OR, odds ratio.

[a]30-Day mortality.

[b]Patients were included if they received at least 2 doses of drugs in the 3 days before or the 14 days after the culture.

[c]OR of 90-day mortality with receipt of piperacillin/tazobactam on univariate analysis.

[d]Risk of 14-day mortality with receiving empirical piperacillin/tazobactam after adjusting for ICU, age, and Pitt bacteremia score in a multivariate analysis.

**Table 2.** Study Data Comparing the Treatment of Extended-Spectrum β-Lactamase Bloodstream Infections With Cefepime Versus Carbapenems.[35-39]

| Study | Size | Cefepime Dosing | Organisms Treated | Infectious Source | Severity | Outcome | Notes |
|---|---|---|---|---|---|---|---|
| Chopra et al[35] (2012) | Empirical n = 57, definitive n = 42 | Not specified | 83% *Klebsiella pneumoniae*, 17% *Escherichia coli* | 75% Catheter | 41% in ICU | In-hospital mortality 33% vs 36% (NS) | No baseline characteristic comparison |
| Lee et al[36] (2013) | n = 178 | 1-2 g q8h | 55% *Enterobacter cloacae*, 24% *Escherichia coli*, 21% *K pneumoniae* | 37% Catheter, 31% primary bacteremia | 70% PBS ≥4 | Increased cefepime 30-day mortality rate 59% vs 17% (*P* = 0.01) | Propensity-matched analysis demonstrated increased mortality with cefepime. Risk was most prominent with elevated cefepime MIC (>1 µg/mL) |
| Siedner et al[37] (2014) | n = 61 (definitive cefepime vs carbapenem) | 66% 2-4 g/d, 14% 6 g/d | *Enterobacter* spp, 78% *Enterobacter cloacae* (overall) | 75% Blood culture positive only, 7% urine (overall) | 70% PBS = 1-4 | In-hospital mortality 17% vs 26% (*P* = 0.25) | Propensity-matched analysis demonstrated no treatment effect |
| Lee et al[38] (2015) | n = 144 | 1-2 g q8h | 100% *Enterobacter cloacae* (73.6% vs 58.3% ESBL producers in definitive carbapenem vs cefepime groups, respectively) | 44% Catheter, 31% urine, 15% pneumonia | 39% PBS ≥4 | 30-Day mortality rate 26.4% cefepime, 22.2% carbapenem (*P* = 0.7) | 2 g q8h Cefepime dose was protective; significantly increased risk of mortality for cefepime-SDD isolates treated with cefepime (HR = 5.55; CI = 2.12-14.53) |
| Wang et al[39] (2016) | n = 68 | 71% 2g q8h, 29% 1g q8h | 62% *K pneumoniae*, 34% *Escherichia coli* | 44% Catheter, 31% urine | 30% ICU, mean PBS = 3 | 14-Day mortality rate 41% cefepime, 20% carbapenem (*P* = 0.08) | All patients treated with carbapenem as definitive therapy; 2 deaths with cefepime MIC of 1 µg/mL |

Abbreviations: ESBL, extended-spectrum β-lactamase; HR, hazard ratio; ICU, intensive care unit; MIC, minimum inhibitory concentration; PBS, Pitt Bacteremia Score; SDD, susceptible dose-dependent.

# Conclusioni della review

- Studi retrospettivi;
- Casistiche limitate;
- Popolazioni di studio eterogenee;
- Possibilità descalation a PTZ o Cefepime , in presenza di patogeni sensibili, quando il focus infettivo ESBL+ è lo apparato urinario oppure addominale , ma in quest' ultimo in paziente non critico;
- In Pz che rispondono a PTZ o Cefepime la terapia può essere continuata senza necessità di escalation a Carbapenemico;
- Il carbapenemico non può essere trascurato nella terapia delle infezioni ESBL+, tuttavia se identifichiamo rapidamente la sorgente infettiva possiamo pensare d'impiegare regimi carbapenem sparing.

PLOS ONE

RESEARCH ARTICLE

# Empiric Piperacillin-Tazobactam *versus* Carbapenems in the Treatment of Bacteraemia Due to Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae

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# Conclusioni dello studio

- La mortalità a 30 gg non presentava differenze significative tra PTZ (29%) e Carbapenemi (17%);
- L’ uso empirico dei carbapenemi era associato più frequentemente a forme senza focus di origine documentato e le infezioni non erano correlate alle cure mediche;
- Sviluppo di complicanze infettive MDRO e/o fungine era maggiore nei trattati con carbapenemici versus PTZ

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Journal of Antimicrobial Chemotherapy

# Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae

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on behalf of the REIPI/ESGBIS/INCREMENT Group‡

**Table 1.** Epidemiological features and predisposing factors of patients with bacteraemia due to ESBL-E in the derivation and validation cohort

| Variable | Derivation cohort ($n = 622$) | Validation cohort ($n = 328$) | *P* value |
|---|---|---|---|
| Median age in years (IQR) | 69 (56–79) | 68 (58–79) | 0.95 |
| Male sex | 353 (57) | 182 (55) | 0.70 |
| Median previous hospital stay in days (IQR)[a] | 2 (0–13) | 1 (0–10) | 0.19 |
| Nosocomial acquisition | 301 (49) | 155 (47) | 0.73 |
| Source | | | 0.56 |
| urinary tract | 274 (44) | 135 (41) | |
| unknown | 108 (17) | 50 (15.1) | |
| biliary tract | 62 (10) | 43 (13) | |
| intra-abdominal | 59 (9) | 43 (13) | |
| vascular | 45 (7) | 20 (6.1) | |
| respiratory tract | 44 (7) | 20 (6.1) | |
| CNS | 1 (0.3) | 0 (0) | |
| osteoarticular | 4 (0.7) | 1 (0.3) | |
| skin and soft tissue | 16 (3) | 11 (3.4) | |
| other | 9 (2) | 5 (2) | |
| Ward admission | | | 0.83 |
| emergency department | 295 (47) | 147 (45) | |
| medical | 165 (27) | 89 (27) | |
| ICU | 91 (15) | 49 (15) | |
| surgical | 71 (11) | 43 (13) | |
| Microorganisms | | | 0.59 |
| *E. coli* | 435 (70) | 218 (66) | |
| *K. pneumoniae* | 133 (21) | 80 (24) | |
| Other *Klebsiella* spp. | 3 (0.5) | 4 (1.2) | |
| *Morganella morganii* | 1 (0.2) | 0 (0) | |
| *Citrobacter freundii* | 3 (0.5) | 2 (0.9) | |
| *Enterobacter cloacae* | 37 (6) | 16 (5) | |
| *Enterobacter aerogenes* | 2 (0.4) | 3 (1) | |
| *Proteus mirabilis* | 5 (0.8) | 2 (0.9) | |
| *Serratia marcescens* | 2 (0.4) | 3 (1) | |
| Other *Enterobacter* spp. | 1 (0.2) | 0 (0) | |
| Median Charlson Index (IQR) | 2 (1–4) | 2 (1–4) | 0.33 |
| Median Pitt score (IQR) | 1 (0–3) | 1 (0–2) | 0.16 |
| Ultimately or rapidly fatal underlying condition | 306 (49) | 173 (52.7) | 0.88 |
| Severe sepsis/septic shock | 224 (36) | 104 (32) | 0.18 |
| Appropriate empirical therapy | 339 (54) | 174 (53) | 0.66 |
| Appropriate targeted therapy | 505 (81) | 265 (81) | 0.88 |
| 30 day crude mortality | 115 (18) | 50 (15) | 0.2 |

Data are expressed as numbers (percentage) except where specified.
[a]Time from admission to positive blood culture.

**Table 2.** Univariate and multivariate analysis of risk factors associated to all-cause 30 day mortality in the derivation cohort with calculated scores

| | Crude analysis | | | | Adjusted analysis | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | No. deceased (%) $n=115$ | No. alive (%) $n=507$ | OR (95% CI) | *P* value | β coefficient | OR (95% CI) | *P* value | Score |
| Age >50 years | 103 (89) | 416 (82) | 1.87 (0.99–3.55) | 0.05 | 0.97 | 2.63 (1.18–5.85) | 0.01 | 3 |
| Male sex | 64 (55) | 289 (57) | 0.94 (0.63–1.42) | 0.79 | | | | |
| Enterobacteriaceae | | | | | | | | |
| *E. coli* | 58 (50) | 377 (74) | 0.35 (0.23–0.53) | <0.001 | | | | |
| *Klebsiella* spp. | 44 (38) | 92 (18) | 2.79 (1.8–4.33) | <0.001 | 0.73 | 2.08 (1.21–3.58) | 0.008 | 2 |
| others | 13 (11) | 38 (7.4) | 1.57 (0.8–3.05) | 0.17 | | | | |
| Nosocomial acquisition | 72 (62) | 229 (45) | 2.03 (1.34–3.08) | 0.001 | | | | |
| Source other than UTI | 91 (79) | 257 (50) | 3.68 (2.27–5.97) | <0.001 | 1.28 | 3.60 (2.02–6.44) | <0.001 | 3 |
| ICU admission | 25 (21) | 46 (9) | 2.78 (1.62–4.76) | <0.001 | | | | |
| Charlson Index ≥2 | 99 (86) | 310 (61.1) | 3.93 (2.25–6.86) | <0.001 | | | | |
| McCabe (UF and RF) | 87 (75) | 219 (43) | 4.08 (2.57–6.47) | <0.001 | 1.36 | 3.91 (2.24–6.80) | <0.001 | 4 |
| Pitt score >3 | 55 (47) | 57 (11) | 7.23 (4.57–11.44) | <0.001 | 1.11 | 3.04 (1.69–5.47) | <0.001 | 3 |
| Severe sepsis/septic shock | 85 (73) | 139 (27) | 7.50 (4.73–11.87) | <0.001 | 1.56 | 4.80 (2.72–8.46) | <0.001 | 4 |
| Inappropriate empirical therapy | 64 (55) | 275 (54) | 1.05 (0.70–1.59) | 0.78 | | | | |
| Inappropriate early targeted therapy | 74 (64) | 80 (15) | 3.22 (2.0–5.0) | <0.001 | 0.90 | 2.47 (1.58–4.63) | 0.002 | 2 |

UTI, urinary tract infection; UF, ultimately fatal; RF, rapidly fatal.

**Score predittivo di mortalità a 30 gg**

**< 11 basso rischio 5,6% (CD) e 5,4% (CV)**

**≥ 11 elevato rischio 45,9% (CD) e 34,8% (CV)**

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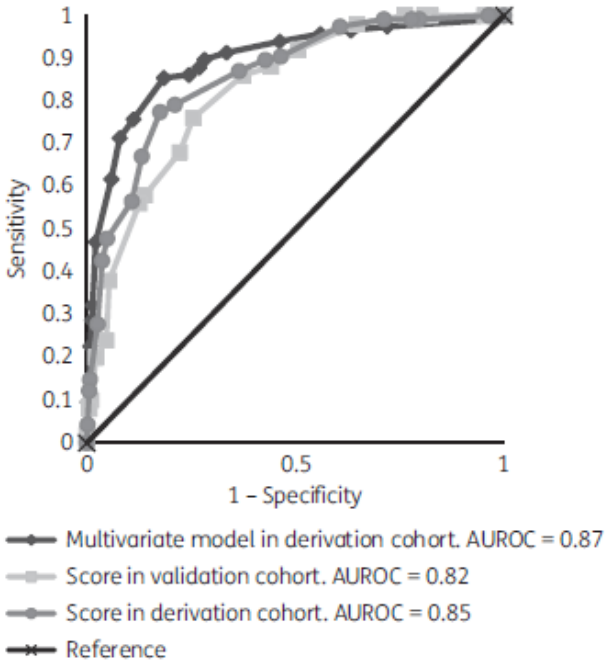


**Figure 1.** Receiver operating curves for the multivariate model and scoring system in the DC and VC.

Harris *et al. Trials* (2015) 16:24
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TRIALS

STUDY PROTOCOL Open Access

# Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible *Escherichia coli* and *Klebsiella* spp (the MERINO trial): study protocol for a randomised controlled trial

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**Methods/Design:** The study will use a multicentre randomised controlled open-label non-inferiority trial design comparing two treatments, meropenem (standard arm) and piperacillin-tazobactam (carbapenem-sparing arm) in adult patients with bacteraemia caused by *E. coli* or *Klebsiella* spp. demonstrating non-susceptibility to third generation cephalosporins. Recruitment is planned to occur in sites across three countries (Australia, New Zealand and Singapore). A total sample size of 454 patients will be required to achieve 80% power to determine non-inferiority with a margin of 5%. Once randomised, definitive treatment will be for a minimum of 4 days, but up to 14 days with total duration determined by treating clinicians. Data describing demographic information, antibiotic use, co-morbid conditions, illness severity, source of infection and other risk factors will be collected. Vital signs, white cell count, use of vasopressors and days to bacteraemia clearance will be recorded up to day 7. The primary outcome measure will be mortality at 30 days, with secondary outcomes including days to clinical and microbiological resolution, microbiological failure or relapse, isolation of a multi-resistant organism or *Clostridium difficile* infection.

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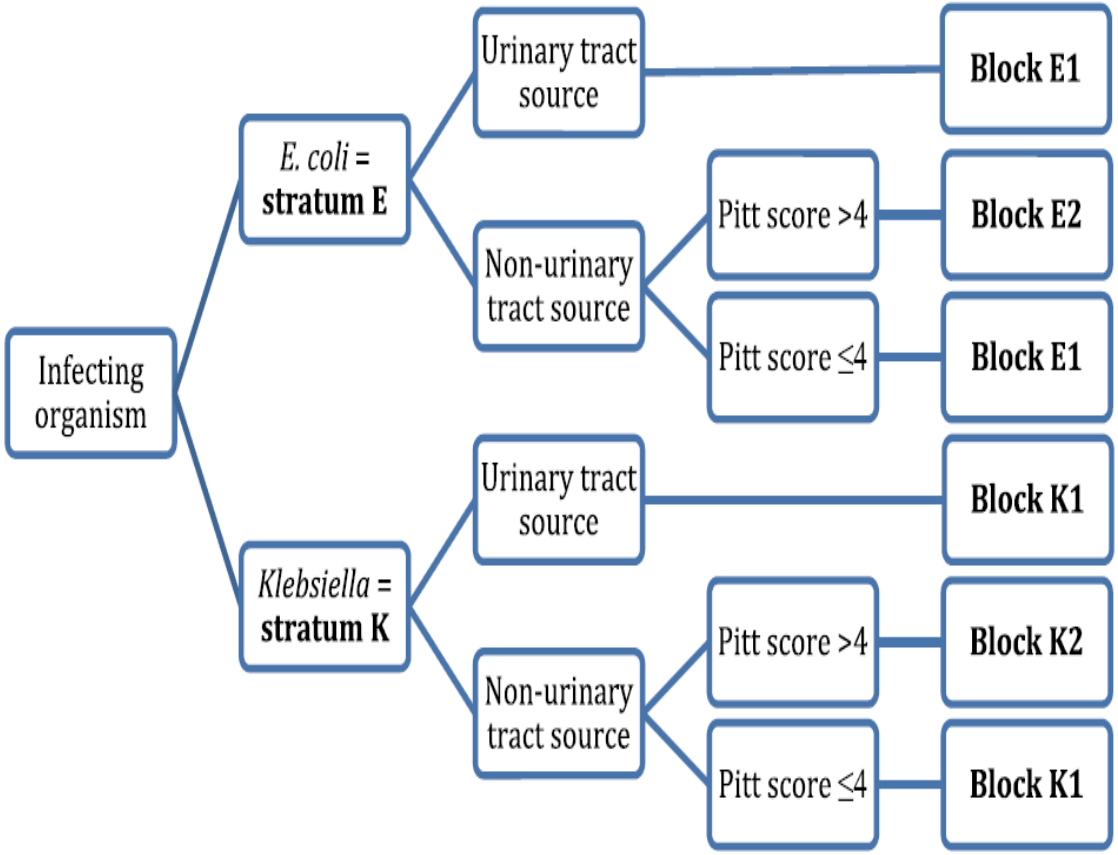


**Figure 1** Patient stratification at enrolment.

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# A Multinational, Preregistered Cohort Study of β-Lactam/β-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae*

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TABLE 1 Characteristics of patients with bloodstream infections caused by extended-spectrum-β-lactamase-producing *Enterobacteriaceae* in the empirical- and targeted-therapy cohorts

| Characteristic | No. (%) of patients (unless otherwise specified) in indicated group | | | | | |
|---|---|---|---|---|---|---|
| | Empirical-therapy cohort | | | Targeted-therapy cohort | | |
| | BLBLI ($n$ = 170) | Carbapenem ($n$ = 195) | $P$ value[a] | BLBLI ($n$ = 92) | Carbapenem ($n$ = 509) | $P$ value[a] |
| Age [median (IQR[b])] | 71.5 (59–79) | 66 (54.5–76) | 0.005[c] | 70.5 (56–80) | 68 (56–78) | 0.22[c] |
| Male sex | 95 (55.9) | 117 (60.0) | 0.42 | 55 (59.8) | 295 (58.0) | 0.74 |
| *Enterobacteriaceae* species | | | | | | |
| *E. coli* | 130 (76.3) | 136 (69.7) | 0.15 | 71 (77.2) | 368 (72.3) | 0.33 |
| *K. pneumoniae* | 29 (17.1) | 45 (23.1) | 0.15 | 13 (14.1) | 101 (19.8) | 0.20 |
| Other | 11 (6.5) | 14 (7.2) | 0.79 | 8 (8.7) | 40 (7.9) | 0.78 |
| Nosocomial acquisition | 75 (44.1) | 91 (46.7) | 0.63 | 38 (41.3) | 247 (48.5) | 0.2 |
| Source | | | | | | |
| Urinary tract | 77 (45.3) | 91 (46.7) | 0.79 | 39 (42.4) | 233 (45.8) | 0.55 |
| Biliary tract | 25 (14.7) | 24 (12.3) | 0.5 | 9 (9.8) | 62 (12.2) | 0.51 |
| Other (high-risk source) | 68[d] (40.0) | 80[e] (41.0) | 0.84 | 44[f] (47.8) | 214[g] (42.0) | 0.30 |
| ICU[h] admission | 13 (7.6) | 26 (13.3) | 0.071 | 4 (4.3) | 62 (12.2) | 0.02 |
| McCabe classification, nonfatal | 81 (47.6) | 95 (48.7) | 0.84 | 47 (51.1) | 263 (51.7) | 0.92 |
| Cancer | 50 (29.4) | 74 (37.9) | 0.068 | 38 (41.3) | 208 (40.9) | 0.86 |
| Pitt score [median (IQR)] | 1 (0–3) | 1 (0–3) | 0.30[c] | 1 (0–2) | 1 (0–2) | 0.19[c] |
| Severe sepsis or shock | 67 (39.4) | 72 (36.9) | 0.86 | 31 (33.7) | 164 (32.2) | 0.94 |
| Targeted therapy with: | | | | | | |
| Carbapenem | 80 (47.1) | 169 (86.7) | <0.0001 | | | |
| BLBLI | 65 (38.2) | 8 (4.1) | <0.0001 | | | |
| Other drug | 25 (14.7) | 18 (9.2) | 0.11 | | | |
| Empirical therapy with: | | | | | | |
| Carbapenem | | | | 4 (4.3) | 141 (27.7) | <0.0001 |
| BLBLI | | | | 56 (60.9) | 140 (27.5) | <0.0001 |
| Other drug | | | | 32 (34.8) | 228 (44.8) | 0.07 |
| Active empirical therapy | | | | 65 (70.7) | 304 (59.7) | 0.047 |
| Cure/improvement | 136 (80.0) | 154 (79.0) | 0.81 | 83 (90.2) | 435 (85.5) | 0.22 |
| 30-day mortality | 30 (17.6) | 39 (20.0) | 0.60 | 9 (9.8) | 71 (13.9) | 0.28 |

[a] $P$ values were calculated by $\chi^2$ test, except where otherwise specified.
[b] IQR, interquartile range.
[c] Mann-Whitney U test.
[d] Other sources included unknown, 21; intra-abdominal, 20; pneumonia, 12; skin, 7; vascular, 7; other, 1.
[e] Other sources included unknown, 27; vascular, 19; intra-abdominal, 16; pneumonia, 10; skin, 5; other, 3.
[f] Intra-abdominal, 17; unknown, 13; vascular, 6; skin, 3.
[g] Unknown, 74; intra-abdominal, 51; vascular, 33; pneumonia, 26; skin, 15; other, 15.
[h] ICU, intensive care unit.

The spread of extended-spectrum-β-lactamase (ESBL)-producing *Enterobacteriaceae* (ESBL-E) is leading to increased carbapenem consumption. Alternatives to carbapenems need to be investigated. We investigated whether β-lactam/β-lactamase inhibitor (BLBLI) combinations are as effective as carbapenems in the treatment of bloodstream infections (BSI) due to ESBL-E. A multinational, retrospective cohort study was performed. Patients with monomicrobial BSI due to ESBL-E were studied; specific criteria were applied for inclusion of patients in the empirical-therapy (ET) cohort (ETC; 365 patients), targeted-therapy (TT) cohort (TTC; 601 patients), and global cohort (GC; 627 patients). The main outcome variables were cure/improvement rate at day 14 and all-cause 30-day mortality. Multivariate analysis, propensity scores (PS), and sensitivity analyses were used to control for confounding. The cure/improvement rates with BLBLIs and carbapenems were 80.0% and 78.9% in the ETC and 90.2% and 85.5% in the TTC, respectively. The 30-day mortality rates were 17.6% and 20% in the ETC and 9.8% and 13.9% in the TTC, respectively. The adjusted odds ratio (OR) (95% confidence interval [CI]) values for cure/improvement rate with ET with BLBLIs were 1.37 (0.69 to 2.76); for TT, they were 1.61 (0.58 to 4.86). Regarding 30-day mortality, the adjusted OR (95% CI) values were 0.55 (0.25 to 1.18) for ET and 0.59 (0.19 to 1.71) for TT. The results were consistent in all subgroups studied, in a stratified analysis according to quartiles of PS, in PS-matched cases, and in the GC. BLBLIs, if active *in vitro*, appear to be as effective as carbapenems for ET and TT of BSI due to ESLB-E regardless of the source and specific species. These data may help to avoid the overuse of carbapenems. (This study has been registered at ClinicalTrials.gov under registration no. NCT01764490.)

## A favore dell utilizzo B-lattamico /inibitore β lattamasi (es. Piperacillina/Tazobactam)

- Frequentemente attiva in vitro su ceppi produttori di ESBL ;
- Sicurezza ed efficacia supportata da studi osservazionali e metanalisi;
- Pressione selettiva con migliore impatto ecologico versus carbapenemi;
- Carbapenemi come ultima linea, in casi estremi, per evitare il circolo vizioso legato al loro eccessivo impiego ( vedi CPE, metallo β - lattamasi);

## Contro l’ impiego B-lattamico /inibitore β lattamasi (es. Piperacillina/Tazobactam) II°

- I carbapenemi rimangono stabili nei confronti delle ESBL;
- Piperacillina/Tazobactam presenta effetto inoculo : aumento della MIC quando la densità microbica aumenta;
- I dati di efficacia contro ESBL derivano soprattutto da studi clinici controllati, nelle infezioni complicate delle vie urinarie;

## Contro l’ impiego B-lattamico /inibitore β lattamasi (es. Piperacillina/Tazobactam) III°

- A tutt’ oggi è stato allestito 1 solo trials clinico di confronto tra piperacillina/tazobactam e carbapenemici;
- Dosi standard di Piperacillina/Tazobactam stentano contro ceppi di enterobatteri ESBL, con MIC con intervallo di sensibilità 8-16 mg/L, soprattutto nel paziente critico;
- Piperacillina/Tazobactam non è attiva su ceppi produttori di AmpC;

# Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche

**Background** Treatment of complicated urinary-tract infections is challenging due to rising antimicrobial resistance. We assessed the efficacy and safety of ceftolozane-tazobactam, a novel antibacterial with Gram-negative activity, in the treatment of patients with complicated lower-urinary-tract infections or pyelonephritis.

**Methods** ASPECT-cUTI was a randomised, double-blind, double-dummy, non-inferiority trial done in 209 centres in 25 countries. Between July, 2011, and September, 2013, hospital inpatients aged 18 years or older who had pyuria and a diagnosis of a complicated lower-urinary-tract infection or pyelonephritis were randomly assigned in a 1:1 ratio to receive intravenous 1·5 g ceftolozane-tazobactam every 8 h or intravenous high-dose (750 mg) levofloxacin once daily for 7 days. The randomisation schedule was computer generated in blocks of four and stratified by study site. The next allocation was obtained by the study site pharmacist via an interactive voice-response system. The primary endpoint was a composite of microbiological eradication and clinical cure 5–9 days after treatment in the microbiological modified intention-to-treat (MITT) population, with a non-inferiority margin of 10%. This study is registered with ClinicalTrials.gov, numbers NCT01345929 and NCT01345955.

**Findings** Of 1083 patients enrolled, 800 (73·9%), of whom 656 (82·0%) had pyelonephritis, were included in the microbiological MITT population. Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure (306 [76·9%] of 398 *vs* 275 [68·4%] of 402, 95% CI 2·3–14·6) and, as the lower bound of the two-sided 95% CI around the treatment difference was positive and greater than zero, superiority was indicated. Adverse event profiles were similar in the two treatment groups and were mainly non-serious.

**Interpretation** Treatment with ceftolozane-tazobactam led to better responses than high-dose levofloxacin in patients with complicated lower-urinary-tract infections or pyelonephritis.

MAJOR ARTICLE

# Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)

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***Background.*** Increasing antimicrobial resistance among pathogens causing complicated intra-abdominal infections (cIAIs) supports the development of new antimicrobials. Ceftolozane/tazobactam, a novel antimicrobial therapy, is active against multidrug-resistant *Pseudomonas aeruginosa* and most extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae.

***Methods.*** ASPECT-cIAI (Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections) was a prospective, randomized, double-blind trial. Hospitalized patients with cIAI received either ceftolozane/tazobactam (1.5 g) plus metronidazole (500 mg) every 8 hours or meropenem (1 g) every 8 hours intravenously for 4–14 days. The prospectively defined objectives were to demonstrate statistical noninferiority in clinical cure rates at the test-of-cure visit (24–32 days from start of therapy) in the microbiological intent-to-treat (primary) and microbiologically evaluable (secondary) populations using a noninferiority margin of 10%. Microbiological outcomes and safety were also evaluated.

***Results.*** Ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in the primary (83.0% [323/389] vs 87.3% [364/417]; weighted difference, −4.2%; 95% confidence interval [CI], −8.91 to .54) and secondary (94.2% [259/275] vs 94.7% [304/321]; weighted difference, −1.0%; 95% CI, −4.52 to 2.59) endpoints, meeting the prespecified noninferiority margin. In patients with ESBL-producing Enterobacteriaceae, clinical cure rates were 95.8% (23/24) and 88.5% (23/26) in the ceftolozane/tazobactam plus metronidazole and meropenem groups, respectively, and 100% (13/13) and 72.7% (8/11) in patients with CTX-M-14/15 ESBLs. The frequency of adverse events (AEs) was similar in both treatment groups (44.0% vs 42.7%); the most common AEs in either group were nausea and diarrhea.

***Conclusions.*** Treatment with ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in adult patients with cIAI, including infections caused by multidrug-resistant pathogens.

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REVIEW Open Access

# The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections

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**Table 4** Antibiotics for treating patients with IAIs based upon susceptibility [253]

| Antibiotic | Enterococci | Ampicillin-resistant enterococci | Vancomycin-resistantenterococci | *Enterobacteriaceae* | ESBL-producing *Enterobactericeae* | *Pseudomonas aeruginosa* | Anaerobic gram-negative bacilli |
|---|---|---|---|---|---|---|---|
| Penicillins/beta-lactamase inhibitors | | | | | | | |
| Amoxicillin/ clavulanate | + | – | – | + | – | – | + |
| Ampicillin/sulbactam | + | – | – | + | – | – | +/– |
| Piperacillin/ tazobactam | + | – | – | + | +/– | + | + |
| Carbapenems | | | | | | | |
| Ertapenem | – | – | – | + | + | – | + |
| Imipenem/cilastatin | +/–[a] | – | – | + | + | + | + |
| Meropenem | – | – | – | + | + | + | + |
| Doripenem | – | – | – | + | + | + | + |
| Fluoroquinolones | | | | | | | |
| Ciprofloxacin | – | – | – | + | – | +[b] | – |
| ––Levofloxacin | +/– | – | – | + | – | +/– | – |
| Moxifloxacin | +/– | – | – | + | – | – | +/– |
| Cephalosporins | | | | | | | |
| Ceftriaxone | – | – | – | + | – | – | – |
| Ceftazidime | – | – | – | + | – | + | – |
| Cefepime | – | – | – | + | +/– | + | – |
| Ceftozolane/ tazobactam | – | – | – | + | + | + | – |
| Ceftazidime/ avibactam | – | – | – | + | + | + | – |
| Aminoglycosides | | | | | | | |
| Amikacin | | | | + | + | + | – |
| Gentamicin | | | | + | + | + | – |
| Glycylcyclines | | | | | | | |
| Tigecycline | + | + | + | +[c] | + | – | + |
| 5-Nitroimidazole | | | | | | | |
| Metronidazole | | | | | | | + |
| Polymixyn | | | | | | | |
| Colistimethate (Colistin) | – | – | – | +[d] | + | + | – |
| Glycopeptides | | | | | | | |
| Teicoplanin | + | + | – | – | – | – | – |
| Vancomycin | + | + | – | – | – | – | – |
| Oxazolidines | | | | | | | |
| Linezolid | + | + | + | – | – | – | – |

[a]Imipenem/cilastatin is more active against ampicillin-susceptible enterococci than ertapenem, meropen and doripenem
[b]Ciprofloxacin is more active against *P. aeruginosa* than levofloxacin
[c]Not active against *Proteus*, *Morganella*, and *Providencia*
[d]Not active against *Morganella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersina* (*Y. enterocolitica*)

**Empiric antibiotic regimens for non-critically ill patients with community-acquired IAIs. Normal renal function**

*Community-acquired cIAIs*

*Non-critically ill patients*

**Amoxicillin/clavulanate 1.2-2.2 g 6-hourly**

or

**Ceftriazone 2 g 24-hourly + Metronidazole 500 mg 6-hourly**

or

**Cefotaxime 2g 8-hourly + Metronidazole 500 mg 6-hourly**

or

In patients with beta-lactam allergy

**Ciprofloxacin 400 mg 8-hourly + Metronidazole 500 mg 6- hourly**

or

**Moxifloxacin 400 24-hourly**

or

In patients at risk for infection with community-acquired ESBL-producing Enterobacteriacea

**Ertapenem 1 g 24 hourly**

or

**Tigecycline 100 mg initial dose, then 50 mg 12-hourly**

# Empiric antibiotic regimens for critically ill patients with community-acquired IAIs. Normal renal function

In patients at risk for infection with community-acquired ESBL-producing Enterobacteriacea

Meropenem 1 g 8-hourly

or

Doripenem 500 mg 8-hourly

or

Imipenem/Cilastatin 1 g 8-hourly

**Empiric antimicrobial regimens for non-critically ill patients with healthcare-associated IAIs. Normal renal function (CrCl>90 mL/min)**

*Healthcare-associated IAIs*

*Non-critically ill patients*

**Piperacillin/Tazobactam 4.5 g 6-hourly**

or

In patients at higher risk for infection with MDROs including recent antibiotic exposure, patient living in a nursing home or long-stay care with an indwelling catheter, or post-operative IAI

**Meropenem 1 g 8-hourly + Ampicillin 2 g 6-hourly**

or

**Doripenem 500 mg 8-hourly + Ampicillin 2 g 6-hourly**

or

**Imipenem/Cilastatin 1 g 8-hourly**

or

As a carbapenem-sparing regimen

**Piperacillin/Tazobactam 4.5 g 6-hourly + Tigecycline 100 mg initial dose, then 50 mg 12-hourly**

+/-

In patients at high risk for invasive candidiasis

**Fluconazole 800 mg LD then 400 mg 24-hourly**

In patients with documented beta-lactam allergy consider use of antibiotic combinations with Amikacin 15–20 mg/kg 24-hourly

# Empiric antimicrobial regimens for critically ill patients with healthcare-associated IAIs. Normal renal function

**Doripenem 500 mg 8-hourly**
or
**Imipenem/Cilastatin 1 g 8-hourly**
or
As a carbapenem-sparing regimen
**Ceftolozane /Tazobactam 1.5 g 8-hourly + Metronidazole 500 mg 6-hourly**
or
**Ceftazidime/Avibactam 2.5 g 8-hourly + Metronidazole 500 mg 6-hourly**
+
**Vancomycin 25–30 mg/kg loading dose then 15–20 mg/kg/dose 8-hourly**
or
**Teicoplanin 12 mg/kg 12-hourly times 3 loading dose then 12 mg/kg 24-hourly**

# ESBL Conclusioni

- Infection control : ospedale, LTF ecc.;
- Valorizzazione dei fattori di rischio : sensibilità diagnostica ecc.;
- Politiche mirate degli antimicrobici:  informazione, educazione, limitazione, uso responsabile ecc.;
- Strategie Terapeutiche a 360 gradi;
- Raccomandazioni di terapia delle principali infezioni basate sull' epidemiologia locale;
- Interventi in zootecnia;
- Interventi in agricoltura ;
- Vaccinazioni ;

# ESBL Conclusioni II°

- I carbapenemi rimangono un'opzione valida;
- L' emergenza di gravi forme di resistenza ne consigliano un impiego limitato e responsabile;
- Piperacillina/Tazobactam può essere utilizzata con una certa tranquillità nelle forme di origine urinaria e dopo attenta valutazione in quelle addominali in pazienti non critici e con MIC utile;
- Regimi terapeutici alternativi come ceftozolano / tazobactam appaiono assai promettenti, per attività battericida e caratteristiche PK/PD.

# Una specie in evoluzione
# l’ importante è evitare l’estinzione