ESBL – Extended Spectrum Beta-Lactamasen

Rainer Gattringer; Institut f. Hygiene u. Mikrobiologie/Infektiologie u. Tropenmedizin

WHO-Liste

- WHO priority pathogens list for R(esearch)&D(evelopement) of new antibiotics

- **Priority 1: CRITICAL**
  - **Acinetobacter baumannii**, carbapenem-resistant
  - **Pseudomonas aeruginosa**, carbapenem-resistant
  - **Enterobacteriaceae**, carbapenem-resistant, **ESBL-producing**

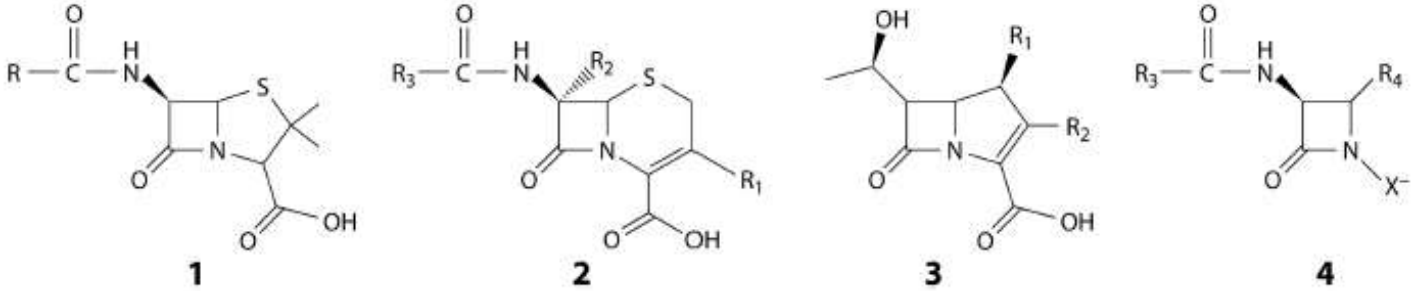


FIG 1 Generic structures of β-lactams most important in clinical medicine. Structures include penicillin (1), cephalosporin (2), carbapenem (3), and monobactam (4).

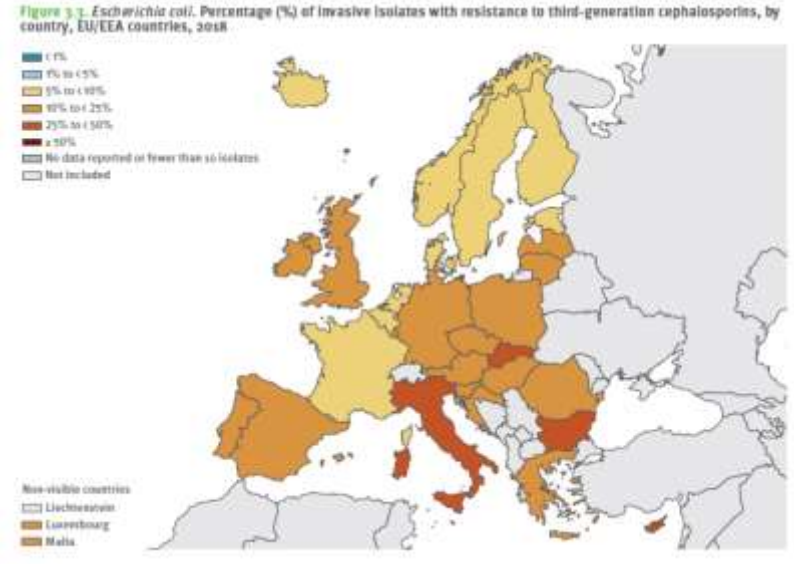
Resistenz gegen Cephalosporine der 3. Generation

- Enterobakterien: sehr häufige Ursache für Infektionen, vor allem im Krankenhaus
- Immer wieder Resistenz gegenüber 3. Cephalosporine

Tabelle 3: Stichprobengrößen und Resistenzraten 2019 der in EARS-Net definierten Bug-Drug-Kombinationen – gramnegative Erreger

	Grampositiv (n = 9.731)			
	Escherichia coli	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Acinetobacter spp.*
Anzahl Isolate (max. Wert)	**7.182**	**1.549**	**909**	**91**
% Resistent				
Aminoglykoside	5,7 (↓)	4,5 (↔)	4,7 (↔)	9,9 (↔)
Aminopenicilline	47,1 (↔)			
Carbapeneme	0,0 (↔)	1,2 (↔)	9,8 (↓)	7,8 (↔)
3.-Generations-Cephalosporine	9,2 (↔)	10,6 (↔)	10,5 (↔)	
Fluorochinolone	18,2 (↔)	16,8 (↑)	11,0 (↔)	11,0 (↔)
Piperacillin/Tazobactam			11,4 (↔)	

↑...Anstieg im 5-Jahres-Trend, ↓...Rückgang im 5-Jahres-Trend, ↔...stabil im 5-Jahres-Trend



Beta-Laktamasen

- **Beta-Laktamasen**
  - **bakterielle Enzyme**
    - die den **Beta-Laktamring von** Beta-Laktamantibiotika **hydrolysieren**
  - **AmpC**
  - **ESBL**
  - Carbapenemasen

Nordmann et al.;
Clin Microbiol Infect 2014; 20: 821–830

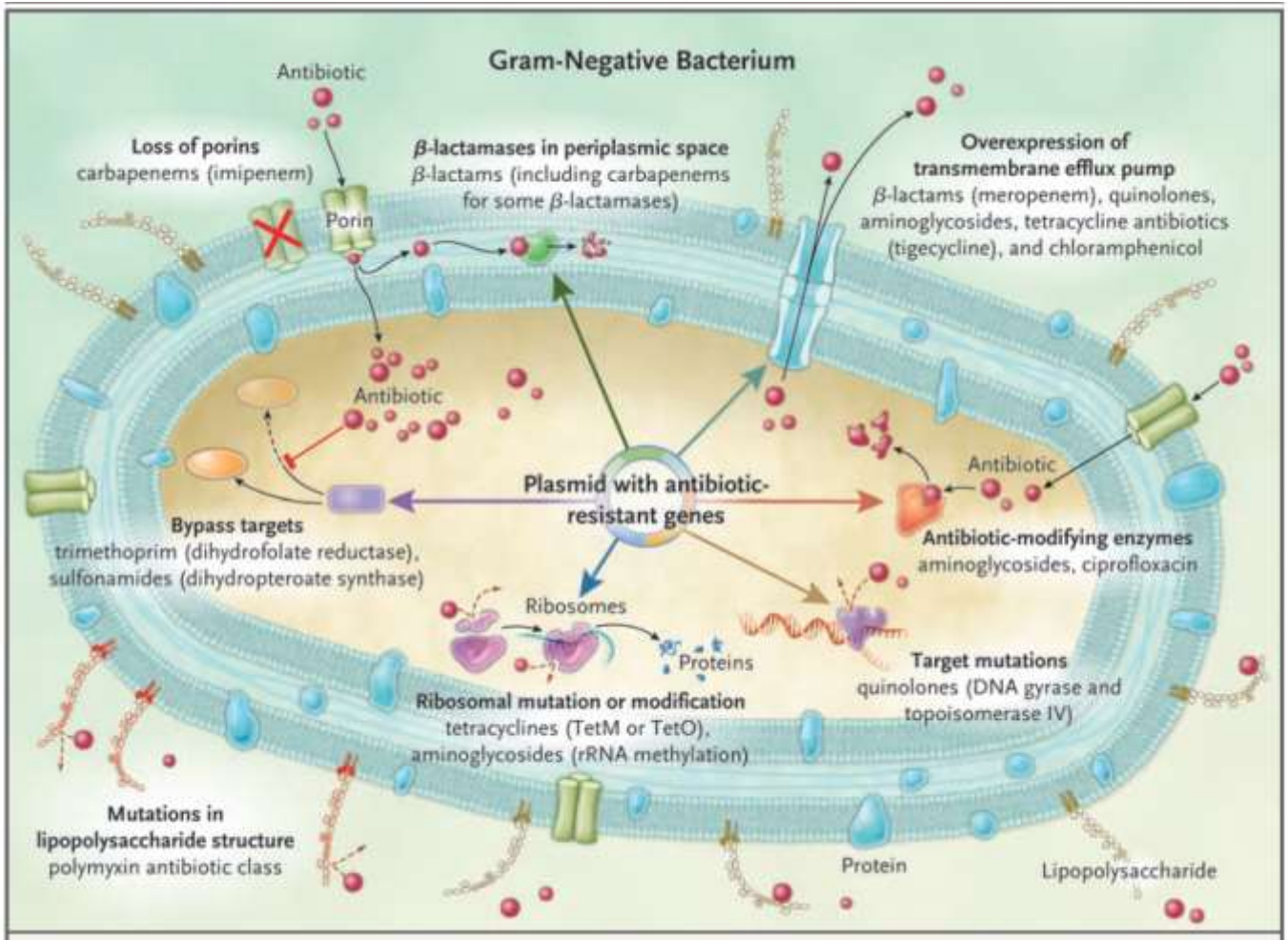


Figure 1. Mechanisms of Resistance in Gram-Negative Bacteria, and the Antibiotics Affected.

Klinikum Wels-Grieskirchen

NEJM

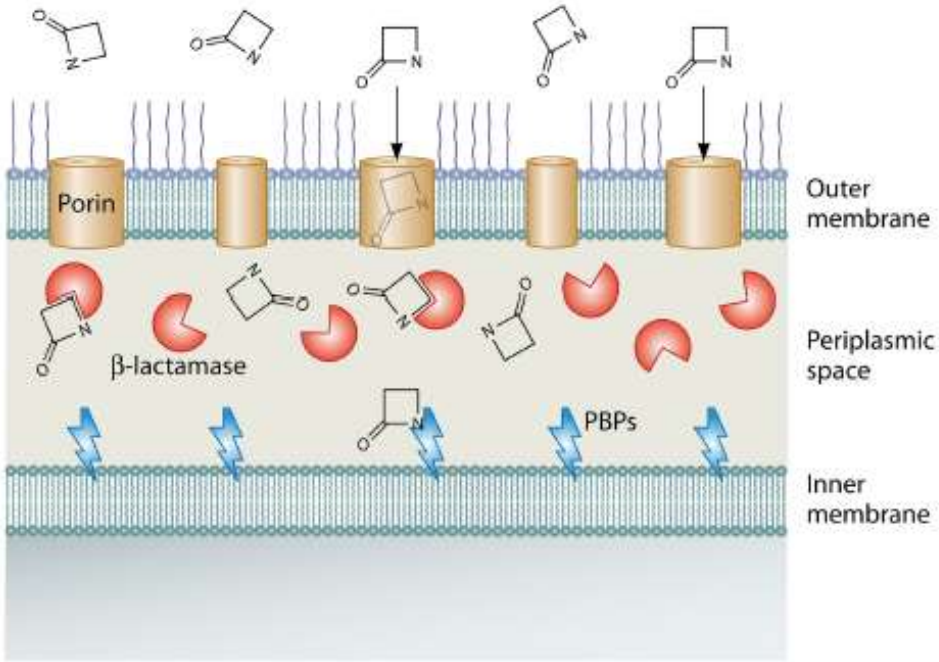


FIG 2 Schematic showing the interaction of β-lactam antibiotics with β-lactam interactive proteins in Gram-negative bacteria.

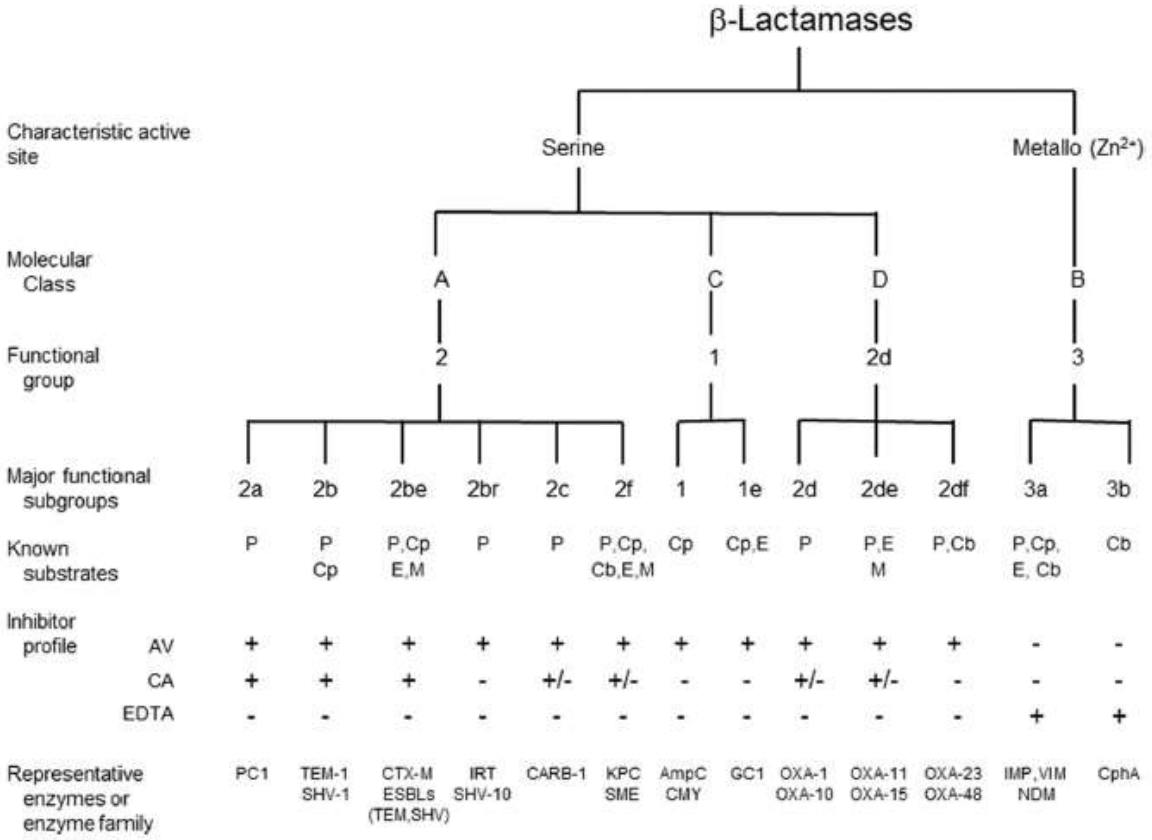


FIG 1 Molecular and functional relationships among β-lactamases (adapted from references 20 and 201 with permission). AV, avibactam; CA, clavulanic acid; Cb, carbapenem; Cp, cephalosporin; E, expanded-spectrum cephalosporin; M, monobactam; P, penicillin.

Resistenz gegen Cephalosporine der 3. Generation

- Häufigsten Ursachen für Resistenz gegenüber 3. Cephalosporinen
  - Enzyme, die antimikrobielle Substanzen beeinflussen/ß-LACTAME
  - **Extended spectrum β-Lactamasen (ESBLs)**
  - **AmpC-type β-Lactamasen**

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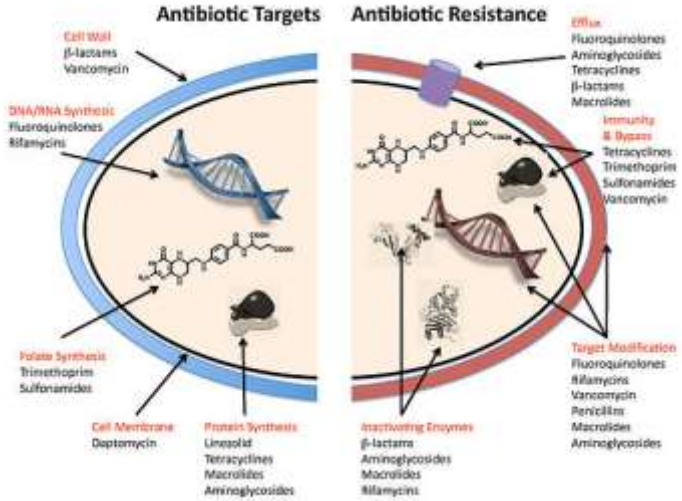

Resistenzmechanismen/Wirksamkeit/Hydrolyse

	C: AmpC	**A:** ESBL	**A**	**B**	**D**
Penicilline					
Cephalosporine I-II					
Cephalosporine III					
Cephalosporine IV					
Carbapeneme					
Monobactame					

Keine (schwache) Hydrolyse

Klinisch relevante Hydrolyse

Nordmann et al.;
Clin Microbiol Infect 2014; 20: 821–830

Extended spectrum β-Lactamasen (ESBLs)

- Enzyme, die ein breites Spektrum von Beta-Laktam-Antibiotika verändern und damit unwirksam machen

- Aminopenicillinen, Cephalosporinen (auch der dritten und vierten Generation), Monobactame

- Haufigsten Gruppen: TEM (Temoniera-lactamase); SHV (sulfhydryl reagent variable-lactamase); CTX-M (cefotaxime-M-ß-lactamase)

- Enzyme liegen auf übertragbaren Genabschnitten
  - Diese können zwischen Bakterien derselben Art oder auch unterschiedlicher Arten ausgetauscht werden (horizontaler Gentransfer)
- Clavulansäure und Tazobactam können ESBL-Enzyme hemmen
- „Reported as is“

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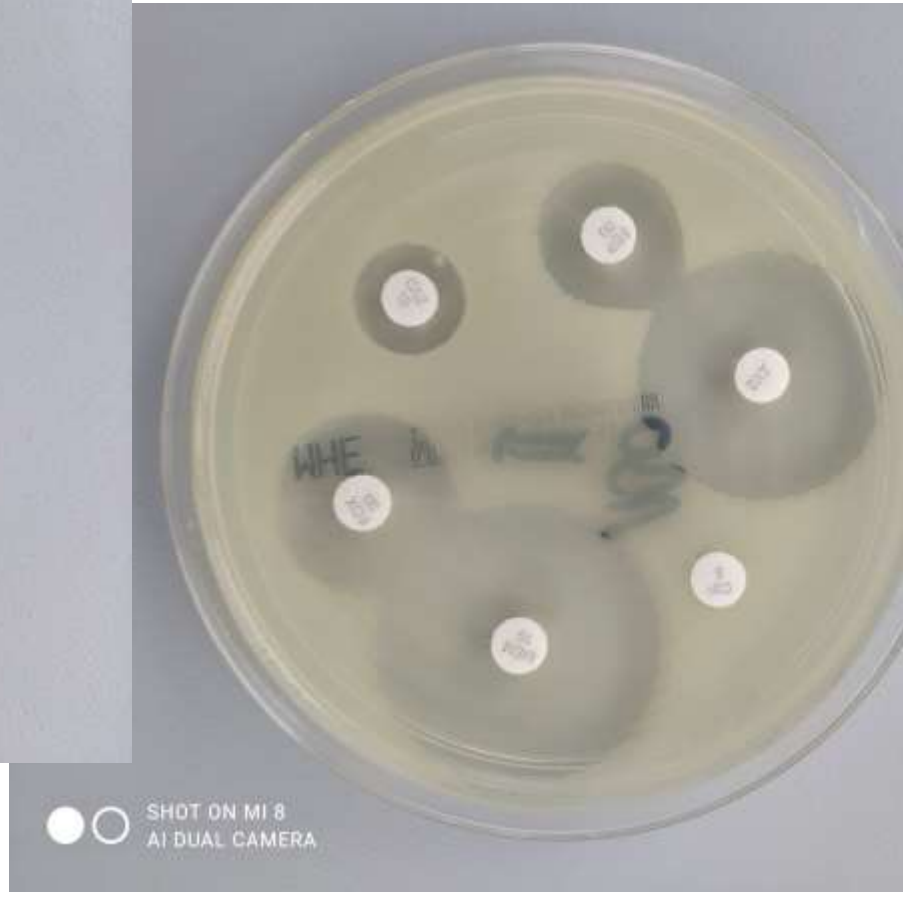
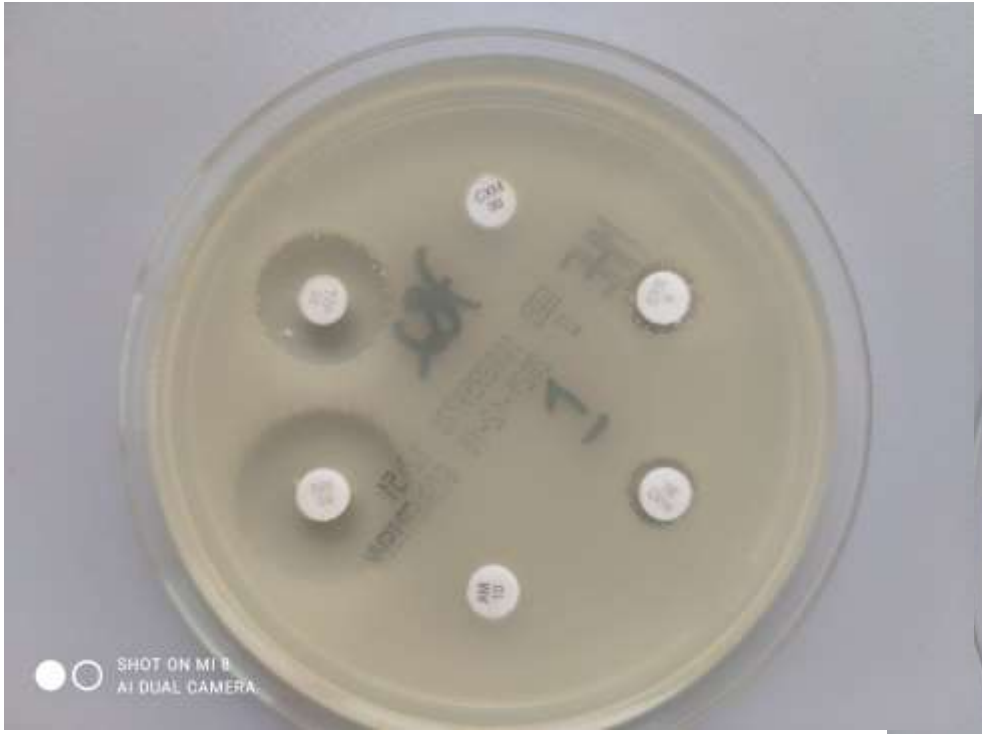


Klinikum
Wels-Grieskirchen



Verschiedenes

- Gleichzeitiges Vorhandensein von Plasmid-kodierten AmpC und ESBL möglich
  - Auch gleichzeitiges Vorhandensein von anderen Resistenz-Mechanismen natürlich auch möglich (z. B.: ESBL + Chinolonresistenz)

- "In Italy, a country endemic for thirdgenerationcephalosporin (3GC)-resistant Enterobacterales, the **ESBL/pAmpC ratio** was found to be approximately **12:1**"
  Euro Surveill. 2017;22:30583

- Unterschiede ESBL – Amp C
  - Amp C keine Hemmung durch gewisse ß-Lactamaseinhibitoren (Clavulans. induz. cAmpC)
  - Amp C Cefepim empfindlich; resistant gegenüber Cefoxitin
  - Amp C im periplasmatischen Raum (Cefepim passiert schnell)

antibiotics

Review

Carbapenem-Sparing Strategies for ESBL Producers: When and How

Ilias Karaiskos * and Helen Giamarellou

Antibiotics **2020**, *9*, 61; doi:10.3390/antibiotics9020061 www.mdpi.com/journal/antibiotics

Piperacillin–Tazobactam

- Interessanteste Alternative zu Carbapenemen

- Tazobactam by itself is a potent ß-lactamase inhibitor

- Tazobactam und Inokulumeffekt

- Datenlage nicht klar
- Viele retrospektive Daten

- Große Unterschiede je nach ESBL-Enzym
- “Reported as is”
- Testung!!!

Klinikum Wels-Grieskirchen

Table 1. Clinical studies comparing the efficacy of piperacillin–tazobactam versus carbapenems in infections caused by ESBL-producing Enterobacterales [10–13,19–30].

Study	Country of Study (Period of Study)	Study Design	PTZ (n, Number of Participants)	Carbapenems (n, Number of Participants)	Organism(s)	Site of Infection	Severity of Illness at Infection Onset	Outcome (PTZ vs Carbapenems)	Comments
Rodríguez-Baño et al. [a] [10]	Spain (2001–2006)	Post hoc analysis of 6 prospective cohorts	Empiric: n = 35 Definitive: n = 18	Empiric: n = 31 Definitive: n = 120	*Escherichia coli* (100%)	BSI (100%) -urinary or biliary (70%)	ICU: 13% Severe sepsis or shock: 23%	**30-day mortality** (empiric): 10% vs 19% (ns) **30-day mortality** (definitive): 9% vs 17% (ns)	No association between either empirical or definitive therapy with PTZ and increased mortality
Kang et al. [19]	Korea (2008–2010)	Retrospective	n = 36	n = 78	*E. coli* (68%) *Klebsiella pneumoniae* (32%)	BSI (100%)	NR	**30-day mortality**: 22% vs 27% (ns)	No difference between PTZ and carbapenem treatment
Tamma et al. [20]	USA (2007–2014)	Retrospective	n = 103	n = 110	*K. pneumoniae* (68%) *E. coli* (31%) *Proteus mirabilis* (1%)	BSI (100%) -CRBSI (46%) -UTI (21%) -cIAI (17%) -Biliary (9%) -pneumonia (9%)	ICU:34% Neutropenia: 15%	**14-day mortality**: 17% vs 8% ($p < 0.05$) **30-day mortality**: 26% vs 11% ($p < 0.01$)	PTZ inferior to carbapenems for the treatment of ESBL bacteremia. Risk of death 1.92 times higher for patients on empiric PTZ therapy
Ober-Friedman et al. [11]	Multicenter (USA, Israel) (2008–2012)	Retrospective	n = 10	n = 69	*E. coli* (53%) *K. pneumoniae* (28%) *P. mirabilis* (19%)	BSI (100%) -pneumonia (34%) -SSTI (28%) -Biliary (17%) -cIAI (9%)	Rapid fatal condition per McCabe score: 39%	**30-day mortality**: 60% vs 34% ($p = 0.10$) **90-day mortality**: 80% vs 48% ($p = 0.05$)	Therapy with PTZ was associated with increased 90-day mortality (adjusted OR, 7.9; $p = 0.03$)
Harris et al. [12]	Singapore (2012–2013)	Retrospective	n = 24	n = 23	*E. coli* (86%) *K. pneumoniae* (14%)	BSI (100%) -UTI (47%) -Biliary (9%)	ICU: 15%	**30-day mortality**: 8% vs 17% (ns)	No difference between PTZ and carbapenem treatment
Gutiérrez-Gutiérrez et al. [a] [13]	INCREMENT international project (2004–2013)	Retrospective	Empiric: n = 123 Definitive: n = 60	Empiric: n = 195 Definitive: n = 509	*E. coli* (73%) *K. pneumoniae* (19%)	BSI (100%) -UTI (45%) -Biliary (12%)	ICU: 11% Severe sepsis or shock: 32%	**30-day mortality** (empiric): 18% vs 20% (ns) **30-day mortality** (definitive): 10% vs 14% (ns)	No association between either empirical or definitive therapy with PTZ and increased mortality
Ng et al. [21]	Singapore (2011–2013)	Retrospective	n = 94	n = 57	*E. coli* (67%) *K. pneumoniae* (33%)	BSI (100%) -UTI (59%) -Biliary (9%) -Pneumonia (9%) -cIAI (5%) -CRBSI (4%)	ICU: 9%	**30-day mortality**: 31% vs 30% (ns)	No difference between PTZ and carbapenem treatment
Gudiol et al.[a] [22]	Multicenter (2006–2015)	Retrospective	Empiric: n = 44 Definitive: n = 12	Empiric: n = 126 Definitive: n = 234	*E. coli* (74%) *K. pneumoniae* (23%) *K. oxytoca* (1.5%) *Enterobacter cloacae* (1.5%)	BSI (100%) -Primary (53%) -CRBSI (16%) -cIAI (15%) -UTI (7%)	ICU: 18% Septic shock: 22% Hematological neutropenic patients: 100%	**30-day mortality** (empiric): 21% vs 13% (ns) **30-day mortality** (definitive): 6% vs 16% (ns)	PTZ appeared to have similar efficacy to carbapenems in hematological neutropenic patients
Seo et al. [23]	Korea (2013–2015)	Randomized trial	n = 33	n = 33	*E. coli* (100%)	UTI (100%) BSI (11%)	Septic shock: 30%	**28-day mortality**: 6.1% vs 6.1% (ns)	PTZ appeared to have similar efficacy to ertapenem in UTIs

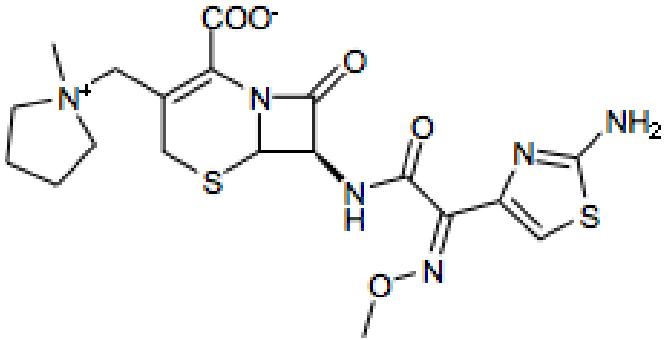
Table 1. *Cont.*

Study	Country of Study (Period of Study)	Study Design	PTZ (n, Number of Participants)	Carbapenems (n, Number of Participants)	Organism(s)	Site of Infection	Severity of Illness at Infection Onset	Outcome (PTZ vs Carbapenems)	Comments
Yoon et al. [24]	Korea (2011–2013)	Retrospective	$n = 68$	$n = 82$	*E. coli* (100%)	UTI (100%) BSI (15%)	ICU: 25% Septic shock: 16%	**In-hospital mortality**: 4.4% vs 13% (ns)	PTZ appeared to have similar efficacy to ertapenem in UTIs
Ko et al. [a] [25]	Korea (2010–2014)	Retrospective	$n = 41$	$n = 183$	*E. coli* (66%) *K. pneumoniae* (34%)	BSI (100%) -Primary (24%) -CRBSI (3%) -UTI (37%) -cIAI (28%)	ICU: 33%	**30-day mortality**: 6.3% vs 11.4% (ns)	No difference between PTZ and carbapenem treatment
Harris et al. [26]	International, multicenter (2014–2017)	Randomized trial	$n = 188$	$n = 191$	*E. coli* (87%) *K. pneumoniae* (13%)	BSI (100%) - UTI (61%) -cIAI (16%) -CRBSI (2%) -Pneumonia (3%) -Mucositis (5%) -SSTI (1%)	ICU: 7% Neutropenia: 7%	**30-day mortality**: 12.3% vs 3.7% ($p = 0.90$)	Definitive treatment with PTZ compared with meropenem did not result in a non-inferior 30-day mortality
Benanti et al. [27]	USA (2008–2015)	Retrospective	$n = 21$	$n = 42$	*E. coli* (100%)	BSI (100%) - cIAI (40%) -UTI (10%) -CRBSI (11%) -Pneumonia (11%) -SSTI (10%)	ICU: 30% Neutropenia: 89%	**14-day mortality**: 0% vs 19% ($p = 0.04$)	Empiric treatment with PTZ not associated with increased mortality in patients with hematologic malignancy
John et al. [28]	USA (2014–2017)	Retrospective	$n = 66$	$n = 51$	*E. coli* (86%) *K. pneumoniae* (14%)	BSI (100%) -UTI (73%) -cIAI (19%) -Pneumonia (1%)	ICU: 38% Septic shock:17%	**In-hospital mortality**: 3% vs 7.8% (ns)	PTZ appeared to have similar efficacy to carbapenems
Nasir et al. [a] [29]	Pakistan (2015–2017)	Retrospective	$n = 89$	$n = 174$	*E. coli* (100%)	BSI (100%) -UTI (66%) -cIAI (23%) -CRBSI (3%)	ICU: 38% Septic shock:17%	**In-hospital mortality**: 13% vs 21% (ns)	PTZ appeared to have similar efficacy to carbapenems
Sharara et al. [30]	USA (2014–2016)	Retrospective	$n = 45$	$n = 141$	*E. coli* (56%) *K. pneumoniae* (30%) *P. mirabilis* (10%) *K. oxytoca* (4%)	UTI (100%)	ICU: 26%	**30-day mortality**: 4% vs 7% (ns)	PTZ appeared to have similar efficacy to carbapenems. Patients treated with carbapenem had higher incident of carbapenem-resistant organism isolated in 60 d ($p = 0.09$)

BSI, blood stream infection; CRBSI, catheter-related blood stream infection; cIAI, complicated intra-abdominal infection; ESBL, extended spectrum β-lactamases; ICU, intensive care unit; NR, not reported; ns, not significant; OR, odds ratio; PTZ, piperacillin–tazobactam; SSTI, skin and soft tissue infections; UTI, urinary tract infection; vs, versus. [a] Studies including β-lactam/β-lactamase inhibitors.

Cefepim

- Bakterizid
- Irreversible Hemmung der Zellwandsynthese
- Breites Spektrum (Gram-negative + Gram-positiv)
- Iv Applikation; 3x2g
- Neurotoxizität
  - Antagonismus y-Aminobuttersäure
  - Eingeschränkte Niere



Cefepim

Table 3. Clinical studies comparing the efficacy of cefepime versus carbapenems in infections caused by ESBL-producing Enterobacterales [23,27,64–71].

Study	Country of Study (Period of Study)	Study design	Cefepime (*n*, Number of Participants) (Dosage)	Carbapenems (*n*, Number of Participants) (Dosage)	Organism(s)	Site of Infection	Severity of Illness at Infection Onset	Outcome (Cefepime vs Carbapenems)	Comments
Zanetti et al. [64]	Six European countries (1997–1999)	Randomized trial	*n* = 13 (2 gr q8h)	*n* = 10 (IMP 500 mg q6h)	*K. pneumoniae* (96%) *E. aerogenes* (4%)	Pneumonia (100%)	ICU (100%)	**Clinical response**: 69% vs 100% ($p < 0.05$)	Comparison for ESBL producers not included
Goethaert et al. [65]	Belgium (1994–2000)	Retrospective	*n* = 21 (2 gr q8h)	*n* = 23 (IMP 500 mg q6h, MEM 1 gr q8h)	*E. aerogenes* (TEM-24)	Pneumonia (64%) BSI (16%) cIAI (14%) UTI (5%) Other (0.3%)	ICU (100%)	**Clinical response**: 62% vs 70% **30-day mortality**: 33% vs 26% (ns)	No statistically significant differences in the outcome for the cefepime and carbapenem-treated groups
Chopra et al. [66]	USA (2005–2007)	Retrospective	Empiric: monotherapy *n* = 43 Definitive: monotherapy *n* = 9 (NR)	Empiric: monotherapy *n* = 14 Definitive: monotherapy *n* = 33 (NR)	*K. pneumoniae* (83%) *E. coli* (17%)	BSI (100%) -CRBSI (75%)	ICU (41%)	**In-hospital mortality** Empiric: 40% vs 36% (ns) Definitive: 33% vs 36% (ns)	Trend toward increased mortality risk with empiric cefepime therapy
Lee et al. [67]	Taiwan (2002–2007)	Retrospective	Empiric: *n* = 21 Definitive: *n* = 17 (1–2 g q8h)	Empiric: *n* = 91 Definitive: *n* = 161 (IMP 500 mg q6h, MEM 1 gr q8h, ETP 1 g q24h)	*E. cloacae* (55%) *E. coli* (24%) *K. pneumoniae* (21%)	BSI (100%) -Primary (14%) -CRBSI (21%) -Pneumonia (24%) -UTI (22%) -cIAI (16%) -SSTI (6%)	McCabe (Rapidly fatal): 11% Pitt score ≥ 4: 67%	**30-day mortality**: Definitive therapy: 59% vs 17% ($p = 0.01$) **Crude mortality**: 65% vs 37% ($p = 0.04$)	Cefepime definitive therapy inferior to carbapenem therapy, 30-day mortality was lower when cefepime MIC≤ 1 mg/L
Wang et al. [68]	USA (2006–2015)	Retrospective	*n* = 17 (1–2 g q8h)	*n* = 51 (IMP 500 mg q6h, MEM 1 gr q8h, ETP 1 g q24h)	*Klebsiella* spp. (63%) *E. coli* (32%) *P. mirabilis* (3%)	BSI (100%) -CRBSI (44%) -UTI (31%) -Biliary (9%) -Pneumonia (15%) -cIAI: (13%) -SSTI: (3%)	ICU (29%)	**14-day mortality**: 41% vs 20% ($p = 0.08$)	Risk of death was 2.87 times higher for patients receiving cefepime compared with carbapenems

Table 3. *Cont.*

Study	Country of Study (Period of Study)	Study design	Cefepime (n, Number of Participants) (Dosage)	Carbapenems (n, Number of Participants) (Dosage)	Organism(s)	Site of Infection	Severity of Illness at Infection Onset	Outcome (Cefepime vs Carbapenems)	Comments
Lee et al. [69]	Taiwan (2008–2012)	Retrospective	Definitive: n = 42 (1–2 g q12h or q8h)	Definitive: n = 53 (IMP 500 mg q6h, MEM 1 gr q8h, ETP 1g q24h)	*E. cloacae* (100%)	BSI (100%) -CRBSI (37%) -Primary (31%) -Pneumonia (9%) -UTI (8%) -cIAI: (8%) -SSTI: (6%)	McCabe (Rapidly fatal): 15% Pitt score ≥ 4: 39%	**30-day mortality**: 26.4% vs 22.2% (ns) **30-day mortality (bacteremia due to ESBL)**: 100% vs 42.9% (p = 0.015)	Comparison for definitive therapy due to ESBL bacteremia with cefepime SDD isolates only reported
Benanti et al. [27]	USA (2008–2015)	Retrospective	n = 40 (2 g q8h)	n = 42 (MEM 1 g q8h)	*E. coli* (100%)	BSI (100%) -CRBSI (19%) -Primary (16%) -Pneumonia (9%) -UTI (7%) -cIAI (43%) -SSTI (6%)	ICU: 26% Leukemia:79% Prior HCT: 50%	**14-day mortality**: 8% vs 19% (ns)	No difference between cefepime and carbapenem therapy
Seo et al. [23]	Korea	Randomized trial	n = 6 (2 g q12h)	n = 33 (ETP 1 g q24h)	*E. coli* (100%)	UTI (100%)	Charlson index: 5 Septic shock: 33%	**Clinical and microbiological response**: 33.3% vs 97% (p < 0.01)	Cefepime therapy inferior to carbapenem therapy
Suh et al. [70]	Korea (2014–2016)	Retrospective	n = 54 (2 g q8h or q12h)	n = 101 (ETP 1 g q24h)	*E. coli* (100%)	UTI (100%)	Charlson index: 2 Septic shock: 6.5%	**In-hospital mortality**: 9.3% vs 9.9% (ns)	No difference between cefepime and carbapenem therapy
Kim et al. [71]	USA (2014–2017)	Retrospective	n = 17 (1–2 g q12h or 2g q8h)	n = 89 (NR)	*E. coli* (82%) *K. pneumoniae* (18%)	UTI (100%)	ICU: 13%	**Clinical and microbiological response**: 100% vs 100% (ns) **Relapse (30-day)**: 0% vs 7%	Comparable effectiveness between cefepime and carbapenems for UTIs

BSI, blood stream infection; cIAI, complicated intra-abdominal infection; CRBSI, catheter-related blood stream infection; ETP, ertapenem; ESBL, extended spectrum β-lactamase; HCT, hematopoietic stem cell transplant; ICU, intensive care unit; IMP, imipenem–cilastatin; MEM, meropenem; NR, not reported; ns, not significant; q24h, every 24 h; q12h, every 12 h; q8h, every 8 h; q6h, every 6 h; SDD, susceptible dose dependent; SSTI, skin and soft tissue infection; UTI, urinary tract infection; vs, versus.

Cefepim und ESBL

In conclusion, the existing literature suggests that cefepime may be suboptimal for invasive ESBL infections. The use of cefepime for serious infection is not safely recommended and has been related to high mortality risk. However, cefepime could be suggested for low-risk infections caused by ESBL (i.e.,UTIs with the supposition of a MIC to cefepime 2 mg/L administrated at a high dose 2 g every 8 h as prolonged infusion).

Andere Möglichkeiten

- Neue Substanzen
- Fosfomycin
- Tigecyclin

- **Testung!!!**
- „Reported as is“

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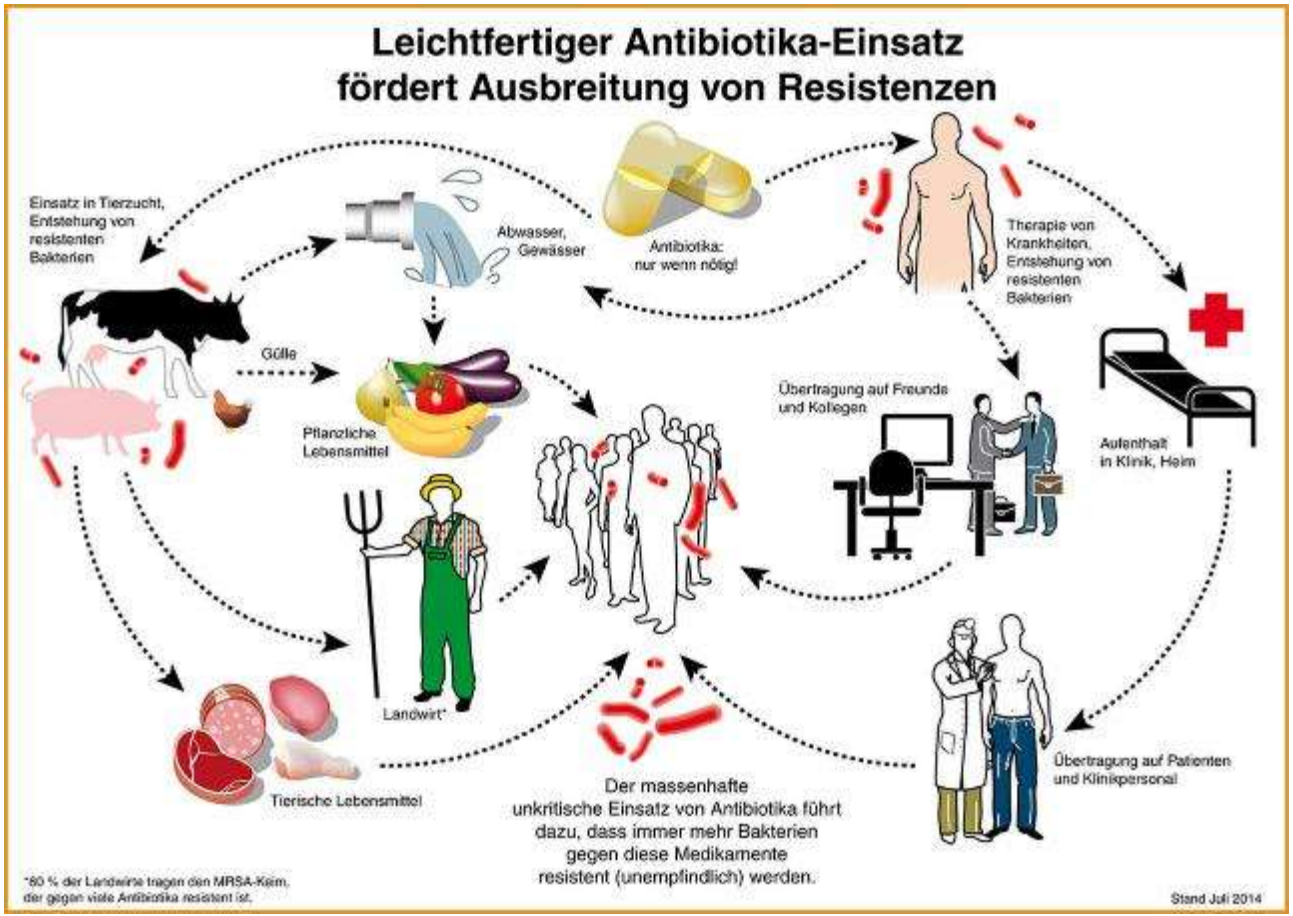

Klinikum Wels-Grieskirchen

ORIGINAL ARTICLE

http://dx.doi.org/10.1590/S1678-9946201759070

Drug resistance, AmpC-β-lactamase and extended-spectrum β-lactamase-producing Enterobacteriaceae isolated from fish and shrimp

Three types of beta-lactamases - ESBL, AmpC and KPC - were investigated. 103 strains were identified, and the most frequent species in shrimp and fish samples was *Enterobacter cloacae* (n = 54). All the strains were resistant to penicillin and more than 50% of the isolates

Zusammenfassung

- **Therapie-Möglichkeit bei Infektionen verursacht durch ESBL-Enterobakterien:**
  - **Pip/Taz, Carbapeneme, Fosfo, Neue Substanzen, Tigecyclin**

- **Empfindlichkeitstestung wichtig**

- **Resistenzmechanismus!**

Klinikum Wels-Grieskirchen

SAVE LIVES
Clean Your Hands

A WHO Patient Safety Initiative

World Health Organization

Klinikum Wels-Grieskirchen

Herzlichen Dank !

Berufung Leben.