ICU ADVANCED
THERAPIE MULTIRESISTENTER KEIME

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MULTIRESISTENZ THERAPIE
ESCKAPE

GRAM+

- **E** NTEROCOCCUS FAECALIS & FAECIUM — INFEKT
- **S** TAPHYLOCOCCUS AUREUS — INFEKT
- **C** LOSTRIDIEN CLOSTRIDIOIDES DIFFICLE — INFEKT

GRAM-

- **K** LEBSIELLA PNEUMONIAE — INFEKT
- **A** CINETOBACTER BAUMANNII — INFEKT
- **P** SEUDOMONAS AERUGINOSA — INFEKT
- **E** SCHERICHIA COLI — INFEKT

Schwerdtner, Urologe 2020

HINWEIS

Wertes Auditorium,

die medizinisch-wissenschaftlichen Informationen dieser Präsentation spiegeln ausschließlich meine eigene Meinung und/oder Erfahrung wider.

Der vollständige Einklang der Inhalte mit den jeweiligen Fachinformationen (Austria Codex) kann daher von Seiten des Sponsors (Zulassungsinhabers) dieser Fortbildungsveranstaltung nicht gewährleistet werden.

MEDIZINISCHE UNIVERSITÄT WIEN

MULTIRESISTENZ THERAPIE
Unsere Sorgenkinder

GRAM-POSITIVE ERREGER

- **Staphylokokken**
  - MRSA
  -
  - (Glykopeptid intermediär)
  - LRS (Linezolid-resistente)
- **Enterokokken**
  - VRE (Vancomycin resistente)
  -
- **Clostridium difficile**

GRAM-NEGATIVE ERREGER

- **Acinetobacter baumanii**
  - 4MRGN
- **Escherichia coli**
  - 3MRGN – ESBL
- **Klebsiella pneumoniae**
  - 3MRGN – ESBL
  - 4MRGN – KPC (NDM-1)
- **Pseudomonas aeruginosa**
  - 4MRGN

PILZE

- **Candida**
  -

MULTIRESISTENZ THERAPIE
Intrinsische Resistenzen

Organisms	Ampicillin/Amoxicillin	Amoxicillin-clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Cefazolin, Cephalothin, Cefalexin, Cefadroxil	Cefoxitin	Cefuroxime	Tetracyclines	Tigecycline	Polymyxin B, Colistin	Fosfomycin	Nitrofurantoin
Citrobacter koseri, Citrobacter amalonaticus	R			R								
Citrobacter freundii	R	R	R		R	R						
Enterobacter cloacae complex	R	R	R		R	R						
Escherichia hermannii	R			R								
Hafnia alvei	R	R	R		R	R				R		
Klebsiella aerogenes	R	R	R		R	R						
Klebsiella oxytoca	R			R								
Klebsiella pneumoniae complex	R			R								
Leclercia adecarboxylata											R	
Morganella morganii	R	R	R		R			R		R		R
Plesiomonas shigelloides	R	R	R									
Proteus mirabilis								R	R	R		R
Proteus penneri	R				R		R	R	R	R		R

EUCAST 2020

MULTIRESISTENZ THERAPIE
Das "I"

	Interpretationskategorie	Bedeutung
S	empfindlich bei Standarddosierung	Therapeutischer Erfolg bei Standarddosierung.
I	empfindlich bei erhöhter Dosierung/Exposition	Therapeutischer Erfolg bei erhöhter Dosierung/Exposition.
R	resistent	Therapeutisches Versagen auch bei erhöhter Dosierung/Exposition.

Exposition des Erregers gegenüber Antibiotikum

- höhere Dosierung (Einzeldosis erhöhen)
- häufigere Verabreichung (Intervall verkürzen)
- veränderte Verabreichungsform (kontinuierliche Gabe)

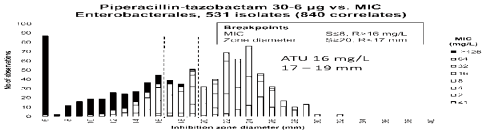
Hinic, Uni Basel 2020 – EUCAST 2020

MULTIRESISTENZ THERAPIE
Intrinsische Resistenzen

Organisms	Ampicillin, Amoxicillin	Amoxicillin-clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Ticarcillin-clavulanic acid	Piperacillin	Piperacillin-tazobactam	Ceftriaxone, Cefotaxime	Ceftazidime	Cefepime	Aztreonam	Ertapenem	Imipenem	Meropenem	Ciprofloxacin	Chloramphenicol	Aminoglycosides	Trimethoprim	Fosfomycin	Tetracyclines	Tigecycline	Polymyxin B/Colistin
Acinetobacter baumannii																						
Acinetobacter pittii	R	R						R			R	R						R	R	R		
Acinetobacter nosocomialis																						
Achromobacter xylosoxidans	R							R				R										
Burkholderia cepacia complex	R	R	R	R	R	R	R	R			R	R			R	R	R	R	R			R
Elizabethkingia meningoseptica	R	R	R	R	R	R		R	R	R	R	R	R	R								R
Ochrobactrum anthropi	R	R	R	R	R	R	R	R	R	R	R	R										
Pseudomonas aeruginosa	R	R	R					R				R				R	Nate	R		R	R	
Stenotrophomonas maltophilia	R	R	R	R		R	R	R			R	R	R	R			R	R	R	R		

EUCAST 2020

MULTIRESISTENZ THERAPIE
ATU – Area of Technical Uncertainty



Infektionserreger	Antibiotikum	MHK (mg/L, ATU)	Hemmhof Durchmesser (mm, ATU)
Enterobacterales	Amoxicillin-Clavulansäure	-	19 - 20
	Piperacillin-Tazobactam	16	17 - 19
	Ceftarolin	-	22 - 23
	Ciprofloxacin	0.5	22 - 24
Pseudomonas aeruginosa	Piperacillin-Tazobactam	-	18 - 19
	Ceftazidim-Avibactam	-	16 - 17
	Colistin	4	-

Hinic, Uni Basel 2020 – EUCAST 2020

MULTIRESISTENZ THERAPIE
Enterokokken (VRE)

- **E. faecalis**
  - 80 – 95%
- **E. faecium**
  - Resistenz! VRE!
- E. casseliflavus
- E. durans
- E. gallinarum
- E. hirae

- **physiologische Darmflora**
  - Mensch und Tier
  - massive Ausscheidg bei Durchfall
    - keine Ursache für Durchfall
    - Umgebungskontamination
- **invasive Infektionen selten**
  - Bakteriämie, Endokarditis
- **Wertigkeit variabel**
  - Harnwegsinfektionen
  - intraabdominelle Infektionen
  - Wundinfektionen
- **keine Therapieindikation**
  - pulmonal

MULTIRESISTENZ THERAPIE
Enterokokken (VRE)

Resistenzphänotyp	VanA	VanB[b]	VanD[b]	VanE	VanG[b]	VanL	VanM	VanN
Vancomycin MHK (in mg/L)	16–1000	4–32 (–1000)	16–512	8–32	16	8	128–>256	12–16
Teicoplanin MHK (in mg/L)	(4–) 16–512	0,5–1	0,5–64[e]	0,5	0,5	E	0,75/96[e]	0,5
Expression	induzierbar	induzierbar	konstitutiv	induzierbar	induzierbar	induzierbar	induzierbar	konstitutiv
Übertragbarkeit	+/–	+/–	–	–	+	–	+	+/–
Vorkommen in *Enterococcus spp.*	*E. faecium* *E. faecalis* *E. durans* *E. hirae* *E. gallinarum*[a] *E. casseliflavus*[a] *E. raffinosus* *E. avium* *E. mundtii* *E. cecorum*	*E. faecium* *E. faecalis* *E. durans* *E. gallinarum*[a]	*E. faecium* *E. faecalis* *E. raffinosus* *E. gallinarum*[a]	*E. faecalis*	*E. faecalis*	*E. faecalis*	*E. faecium*	*E. faecium*

E empfindlich (keine MHK angegeben)
[a]Erwerb von *vanA-*, *vanB-* oder *vanD-* Genen zusätzlich zu *vanC1/vanC2* (selten), das *vanB*-Gen hat auch ein Reservoir in anaeroben Darmkommensalen (keine Enterokokken)
[b]Subtypen existieren (*vanB1–3*, *vanD1–5*, *vanG1–2*)
[e]verschiedene VanD- bzw. VanM-Stämme zeigten variable Teicoplanin MHK-Werte

KRINKO, Bundesgesundheitsbl 2018

MULTIRESISTENZ THERAPIE
Enterokokken (VRE)

Intrinsische Resistenzen
- Alle Cephalosporine
- Penicillinasestabile Penicilline (z. B. Flucloxacillin, Methicillin)
- Polymyxine (z. B. Colistin)
- Fluorchinolone (z. B. Levofloxacin) nur *E. faecium*
- Lincosamide (z. B. Clindamycin)
- Mupirocin nur *E. faecalis*
- Aminoglykoside (z. B. Gentamicin), bei Low-level-Resistenz Kombinationstherapie mit Ampicillin durch Synergismus wirksam

Erworbene Resistenzen
- Beta-Lactam-Antibiotika (z. B. Ampicillin, Carbapeneme), sehr häufig bei *E. faecium*, selten bei *E. faecalis*
- Makrolide (z. B. Erythromycin)
- Aminoglykoside (z. B. Gentamicin), High-level-Resistenz
- Fluorchinolone (z. B.Levofloxacin), High-level-Resistenz
- Tetracycline und Glycylcline (z. B. Tigecyclin)
- Glykopeptide (z. B. Vancomycin), häufig bei *E. faecium*, selten bei *E. facalis*
- Oxazolidinone (z. B. Linezolid)
- Lipopeptide (Daptomycin), bisher sehr selten (<0,1 %)

Pochhammer, Chirurg 2017

MULTIRESISTENZ THERAPIE
Staphylococcus aureus

Penicillin	PLUS	ALLE β-Laktame sind EMPFINDLICH
Oxacillin	PLUS	
Penicillin	NEGATIV	Penicillin, Ampicillin, Mezlocillin, Piperacillin RESISTENT
Oxacillin	PLUS	ALLE anderen β-Laktame EMPFINDLICH
Penicillin	NEGATIV	→ MRSA!!!
Oxacillin	NEGATIV	Penicilline, Cephalosporine, Carbapeneme RESISTENT

MULTIRESISTENZ THERAPIE
Staphylococcus aureus

- **Cefazolin**
- **Flucloxacillin**
- **Levofloxacin**
- **Moxifloxacin**

- **Piperacillin/Tazobactam**
  - höhere Mortalität
  - inoculum-Effekt?
  - KEINE MSSA-Monotherapie!

Beganovic, Open Forum Infect Dis 2019

MULTIRESISTENZ THERAPIE
Staphylococcus aureus

Auswahl der Antibiotikatherapie darf nicht nur von der
- **"in vitro" Empfindlichkeit**
- **Preis**

abhängen, sondern muss auch
- **Infektionsort**
- **Schwere der Infektion**
- **Toxizität**

berücksichtigen.

UNKOMPLIZIERTE INFEKTIONEN
- KEINE septischen Streuherde
- KEIN Hinweis auf Endokarditis
- KEINE tiefsitzende Infektionsherde
- ENTFIEBERUNG innerhalb von 48 – 72 Std
- KEINE Fremdkörper wie TEP, PE, TAVI etc
- NEGATIVE Blutkultur 48 – 96 Std nach ABT-Beginn

KEINE KOMBINATIONSTHERAPIE

KOMPLIZIERTE INFEKTIONEN
- Stuhlen
- Dauer bis zur Sterilität
- Dosierung
- Eindringtiefe Evidenz
- Fremdkörper
- Inoculum
- Problemkeime
- Synergismus
- Toxinbildung

KOMBINATIONSTHERAPIE

Kimmig, Front Med 2021

MULTIRESISTENZ THERAPIE
Staphylococcus aureus

Trimethoprim-sulfamethoxazole	1–2 double-strength tablets (160/800 mg) every 12 h
Doxycycline	100 mg every 12 h
Minocycline	100 mg every 12 h
Rifampin	600 mg every day
Clindamycin	300–600 mg every 6-8 h (pediatric dosage, 2-8 mg/kg every 6-8 h)
Linezolid	400–600 mg every 12 h
Fusidic acid (usually given in combination with rifampin)	500 mg every 8 h

- **ambulante Infektionen**
- **Kinder, junge Erwachsene**
- **primär gesunde Patienten**
- **KEINE Multiresistenz**
- ***SCCmec* Typ IV, V**
- **PVL-positive Stämme sind VIRULENTER als andere MRSA oder MSSA-Stämme**
- **Clindamycin, Linezolid**

CA-MRSA

Moellering, Clin Infect Dis 2008 – Nathwani, J Antimicrob Chemother 2008

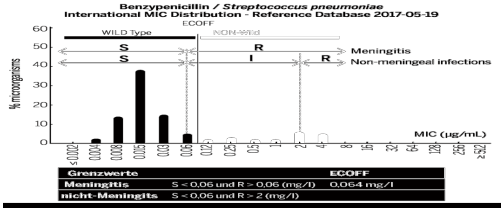
MULTIRESISTENZ THERAPIE
Streptococcus pneumoniae

Erreger	AmpC	TEM 1, 2 SHV 1	ESBL: TEM- und SHV-Varianten	ESBL: CTX-M-Varianten u.a.	Metallo-enzyme	Penicillinasen (Gr. 2a)
Staphylokokken						◆◆◆
Pneumokokken	KEIN BETALAKTAMASEINHIBITOR NOTWENDIG !					
Enterokokken						
Gonokokken		◆◆				
Haemophilus		◆				
Escherichia coli	◆	◆◆◆	◆◆	◆		
Klebsiella pneumoniae	◆	◆◆	◆◆	◆	◆	
Proteus mirabilis	◆	◆◆	◆◆	◆◆		
Enterobacter sp.	◆◆◆	◆	◆◆	◆◆	◆	
Pseudomonas	◆	◆	◆	◆	◆	
Acinetobacter	◆◆	◆	◆		◆	

Häufigkeit: ◆◆◆ stark ◆◆ mittel ◆ gering

Theuretzbacher, Pharmazie aus unserer Zeit 2006

MULTIRESISTENZ THERAPIE
Streptococcus pneumoniae

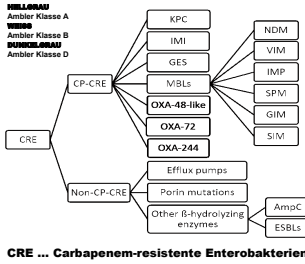


Grenzwerte	ECOFF
Meningitis	S < 0.06 und R > 0.06 (mg/l) 0.064 mg/l
nicht-Meningitis	S < 0.06 und R > 2 (mg/l)

> Der epidemiologische Cut-off (ECOFF) ermöglicht die Unterscheidung zweier Populationen nach MHK-Werten in "Wildtyp" und "Nicht-Wildtyp".

www.eucast.com

MULTIRESISTENZ THERAPIE
Betaläktamasen

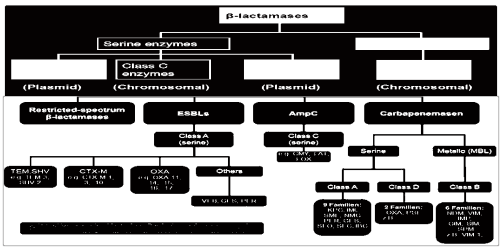


Species	Class A	Class B (MBLs)	Class D
Klebsiella pneumoniae	KPC-3	NDM-1, VIM-1	OXA-48
Klebsiella oxytoca			OXA-48, OXA-181
Enterobacter cloacae	KPC	NDM-1, NDM-9, NDM-9, VIM	OXA-48, OXA-181, OXA-244
Pseudomonas aeruginosa	KPC		OXA-48
Serratia marcescens	KPC	VIM	
Citrobacter freundii	KPC, DD-1	VIM-4	OXA-48
Enterobacter aerogenes	KPC		OXA-48
Citrobacter freundii		VIM	OXA-48
Citrobacter koseri			OXA-48
Salmonella enterica	KPC-2	NMD-1, NMDA, VIM-1, VIM-2, IMP-4	OXA-48
Morganella morganii		NDM-1	OXA-48
Providencia stuartii	KPC-2	VIM-1	
Providencia rettgeri		IMP-4	OXA-72

CRE ... Carbapenem-resistente Enterobakterien

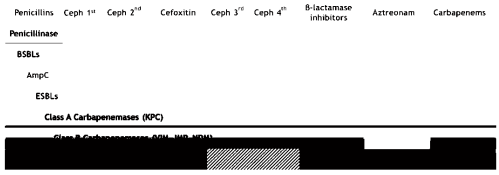
Suay-García, Antibiotics 2019

MULTIRESISTENZ THERAPIE
Betalaktamasen



Bush, Rev Inf Dis 1987 – Bush, Antimicrob Agents Chemother 1959 – Bradford, Clin Microbiol Rev 2001
Bush, Curr Opin Investig Drugs 2002 – Jacoby, Clin Microbiol Rev. 2009 – Stuart, Int J Antimicrob Agents. 2010

MULTIRESISTENZ THERAPIE
Aktivität & Resistenz im Vergleich



Kakoullis, Antibiotics 2021

MULTIRESISTENZ THERAPIE
Resistenz & Umgang in der Praxis

- **IGNORIEREN**
  - Kontamination
  - Kolonisation
- **ISOLIEREN**
  - asymptomatisch
  - symptomatisch
  - krankenhaushygienisch
- **EIN PROBLEM HABEN**
  - Infektion

MULTIRESISTENZ THERAPIE
Penicillin G

- ***Staphylococcus aureus***
  - 50% resistente Stämme nach 5 Jahren bei niedrigem Selektionsdruck
  - 70 – 80% Resistenzrate heute weltweit
- ***Streptococcus pneumoniae***
  - 1962 erstmals beschrieben
  - <1 bis 50% resistente Stämme heute
  - regionale Unterschiede
- ***Streptococcus pyogenes***
  - trotz hohem Selektionsdruck weltweit kein resistenter Stamm beschrieben

MULTIRESISTENZ THERAPIE
AWaRe

Antibiotika sortiert nach AWaRe-Gruppen und Verbrauch 2018

	ATC-Antibiotikum	%
	Amoxicillin und Beta-Lakatmase Inhibitor	27,3
	Doxycyclin	8,0
	Ciprofloxacin	7,9
	Cefuroxim	5,9
	Azithromycin	5,2
	Amoxicillin	5,0
	Clindamycin	4,8
	Phenoxymethylpenicillin	4,7
	Ciprofloxacin	4,4
	Cefalexin	2,4
	Nitrofurantoin	2,0
	Moxifloxacin	1,9
	Levofloxacin	1,8
	Cefaclor	1,8
	Ampicillin und Beta-Lakatmase Inhibitor	1,7
	Piperacillinum	1,6
	Trimethoprim	1,6
	Cefpodoxim	1,1
	Minocyclin	1,0
	Metronidazol	0,8
	Sulfamethoxazol und Trimethoprim	0,7
	Piperacillin und Beta-Lakatmase Inhibitor	0,7
	Meropenem	0,6
	Cefixime	0,6
	Tetracyclin	0,6
	Azithromycin	0,5
	Pivmecillinam	0,5
	Fosfomycin	0,5
	Cefazolin	0,5
	Fosfomycin	0,5
	Sulfamethoxazol	0,4

	Flucloxacillin	0,4
	Benzylpenicillin	0,4
	Linezolid	0,3
	Sulfamethoxazol und Trimethoprim	0,2
	Cefotaxim	0,2
	Norfloxacin	0,2
	Cefazolin	0,2
	Furadantinum	0,2
	Tobramycin	0,1
	Cefotaxim	0,1
	Erythromycin	0,1
	Vancomycin	0,1
	Doxycycline	0,1
	Ofloxacin	0,1
	Imipenem und Cilastatin	0,1
	Teicoplanin	0,1
	Ceftriaxon	0,1
	Ampicillin	0,1
	Cefotaxim	0,1
	Gentamicin	0,1
	Tigecyclin	0,1
	Azithromycin	0,0
	Ertapenem	0,0
	Aztreonam	0,0
	Ceftazidim und Beta-Lakatmase Inhibitor	0,0
	Ceftolozan und Beta-Lakatmase Inhibitor	0,0
	Sulfadiazin	0,0
	Cefiderocol Intravenös	0,0
	Dalbavancin	0,0
	Tedizolid	0,0
	Ceftaroline	0,0
	Ceftobiprol Medocaril	0,0

Access Gruppe, Watch Gruppe, Reserve Gruppe, Nicht klassifiziert

Access verwenden

Watch beobachten

Reserve vorhalten

Allerberger, ÖÄZ 2019

MULTIRESISTENZ THERAPIE
Cefazolin & Co

ALT, BILLIG, GUT – MSSA

- Cefazolin
- Clindamycin
- Cotrimoxazol
- Doxycyclin
- Flucloxacillin
- Fusidinsäure
- Minocyclin
- Moxifloxacin
- Trimethoprim

KOMBINATIONSPARTNER

- Fosfomycin
- Rifampicin

NEU, TEUER, BESSER – MRSA

- Ceftobiprol
- Ceftarolin
- Dalbavancin
- Daptomycin
- Delafloxacin
- ◄ Linezolid
- Oritavancin
- ◄ Teicoplanin
- Tedizolid
-
- Tigecyclin
- ◄ Vancomycin

MRSA 6.4% 2019

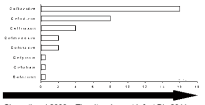
MULTIRESISTENZ THERAPIE
Cefazolin & Co

- **Cefazolin**
- **Flucloxacillin**
- **Delafloxacin**
- **Moxifloxacin**

CEPHALOSPORINE

- **Cefazolin**
  - tiefe Kompartimente
  - hohe Bakterienlast (Inoculum)
- **Cefotaxim & Ceftriaxon**
  - aufgrund höherer MHK weniger aktiv als Penicillin?

- **Piperacillin/Tazobactam**
  - höhere Mortalität
  - inoculum-Effekt?
  - KEINE MSSA-Monotherapie!



Rayner, Int Med J 2005 – Fernandez-Guerrero, Clin Infect Dis 2005 – Wiedemann, Chemother J 2008 – Thwaites, Lancet Infect Dis 2011
Beganovic, Open Forum Infect Dis 2019

MULTIRESISTENZ THERAPIE
Ceftarolin & Co

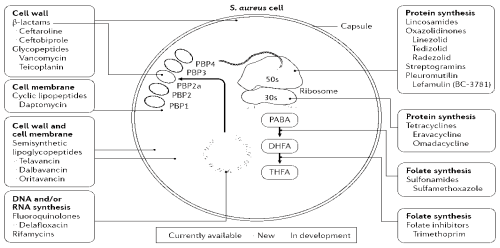
	Tedizolid	Linezolid	Dalbavancin	Oritavancin	Telavancin	Vancomycin
MSSA	0.5	2–4	0.06	0.06	0.06	1
MRSA	0.5	2–4	0.06	0.06	0.06	1
VISA	0.5	4	0.5–2	1	0.12	8
hVISA	0.5	1	0.5	2	0.12	2
Linezolid-resistant *S. aureus* (*cfr*-gene mediated resistance)	0.5–1	8–32			0.06	1
Linezolid-resistant *S. aureus* (23S rRNA mutations)	8	>32			0.06	2
Coagulase-negative staphylococci	0.5	1–2	0.06–0.12	0.06	0.06	2
Vancomycin-susceptible *E. faecalis*	1	2	0.06	0.03	0.12	2
Vancomycin-resistant *E. faecalis*	0.5	2	>4	0.03–0.5	>2	>32
Vancomycin susceptible *E. faecium*	1	2–4	0.12	≤0.008	0.04	1
Vancomycin-resistant *E. faecium*	0.5	2	>4	≤0.008–0.12	3	>32
Streptococcus pneumoniae	0.25	1	0.03	≤0.008	≤0.015	0.5
β-Hemolytic *Streptococcus*	0.5	1	≤0.03	0.12	0.04	0.5
Viridans group *Streptococcus*	0.25	1	≤0.03	0.03–0.06	0.03	1

MIC (mg/L)

Strain	ceftaroline	ceftriaxone	ceftobiprole	daptomycin	linezolid	tigecycline	vancomycin
MSSA 89008	0.12	4	0.25	0.12	2	0.25	1
MSSA 89027	0.12	2	0.25	0.12	1	0.12	1
CA-MRSA 83771	0.5	128	1	0.25	2	0.25	1
HA-MRSA 86495	0.5	64	1	0.12	2	0.25	1
hVISA 86775	0.5	128	1	0.25	2	0.5	1
VISA NRS18	1	32	2	0.5	2	0.25	4
VISA NRS21	0.5	128	1	0.5	1	0.06	2
VISA NRS4	1	128	1	0.5	1	0.25	4
VRSA VRS1	1	128	2	0.25	2	0.5	64
VRSA VRS3a	0.5	128	1	0.12	2	0.12	64

Biedenbach, Antimicrob Agents Chemother 2009 – Keel, Antimicrob Agents Chemother 2011 – Flamm, Clin Microbiol Infect 2012
Farrell, Clin Microbiol Infect 2012 – Boucher, N Engl J Med 2014 – Chan, AAC 2015 – Lahiri, JAC 2016 – Crotty, J Clin Microbiol 2016

MULTIRESISTENZ THERAPIE
Staphylokokken (MRSA)



Lee; Nat Rev 2018

MULTIRESISTENZ THERAPIE
Daptomycin

No. of Days of Bacteremia	Total N	Mortality, %	Relative Risk (95% CI) Reference	Relative Risk (95% CI) Reference	P Value
1	446	3.5			
2	108	8.3	1.86 (0.87–3.97)		.11
3	98	9.2	2.05 (0.96–4.36)		.06
4	74	12.2	2.71 (1.28–5.73)		.01
5	46	8.7	1.94 (0.69–5.43)		.21
6	33	18.2	4.05 (1.75–9.40)		.001
7	28	21.4	4.78 (2.09–10.94)		<.001
8–10	30	20.0	4.46 (1.94–10.27)		<.001
11+	21	23.8	5.31 (2.21–12.76)		<.001
Per day			1.16 (1.10–1.23)		<.001

Characteristics	Value
Dapto + Ceftaroline Salvage	8 (31%)
2nd line	13 (50%)
3rd line	5 (19%)
4th line	
Dapto dosing	
4 mg/kg	1 (4%)
6 mg/kg	7 (27%)
≥ 8 mg/kg	18 (69%)
Ceftaroline Dosing	
Q 8 hr	5 (19%)
Q 12 hr	19 (73%)
Q 24 hr	2 (8%)
DAP + CPT median d (range)	42 (3-61)
> 7 days	23 (88%)
> 28 days	7 (28%)
Bacteremia prior to DAP + CPT	10 d (3-23)
Bacteremia after DAP + CPT	2 d (1-6)

Daptomycin – Ceftarolin

Sakoulas, Clin Ther 2014 – Minejima, Clin Infect Dis 2019

MULTIRESISTENZ THERAPIE
Daptomycin

Cloxacillin or fosfomycin plus daptomycin combinations are more active than cloxacillin monotherapy or combined with gentamicin against MSSA in a rabbit model of experimental endocarditis

Background: *In vitro* and *in vivo* activity of daptomycin alone or plus either cloxacillin or fosfomycin compared with cloxacillin alone and cloxacillin plus gentamicin were evaluated in a rabbit model of MSSA experimental endocarditis (EE).

Methods: Five MSSA strains were used in the *in vitro* time–kill studies at standard (10^5–10^6 cfu/mL) and high (10^8 cfu/mL) inocula. In the *in vivo* EE model, the following antibiotic combinations were evaluated: cloxacillin (2 g/4 h) alone or combined with gentamicin (1 mg/kg/8 h) or daptomycin (6 mg/kg once daily); and daptomycin (6 mg/kg/day) alone or combined with fosfomycin (2 g/6 h).

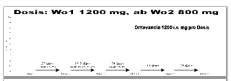
Results: At standard and high inocula, daptomycin plus fosfomycin or cloxacillin were bactericidal against 4/5 and 5/5 strains, respectively, while cloxacillin plus gentamicin was bactericidal against 3/5 strains at standard inocula but against none at high inocula. Fosfomycin, cloxacillin, gentamicin and daptomycin MIC/MBCs of the MSSA 6/8 strain used in the EE model were 8/16, 0.25/0.5, 0.25/0.5 and 1/8 mg/L, respectively. Adding gentamicin to cloxacillin significantly reduced bacterial density in vegetations compared with cloxacillin monotherapy ($P = 0.026$). Adding fosfomycin or cloxacillin to daptomycin (10/11 (93%) and 8/11 (73%), respectively) significantly improved the efficacy of daptomycin in sterilizing vegetations (0/11 (0%), $P < 0.001$ for both combinations) and showed better activity than cloxacillin alone (0/10 (0%), $P < 0.001$ for both combinations) and cloxacillin plus gentamicin (3/10 (30%), $P = 0.086$ for cloxacillin plus daptomycin and $P = 0.008$ for fosfomycin plus daptomycin). All recovered isolates showed increased daptomycin MIC.

Conclusions: The addition of cloxacillin or fosfomycin to daptomycin is synergistic and rapidly bactericidal, showing better activity than cloxacillin plus gentamicin for treating MSSA EE, supporting their clinical use.

García-de-la-María, J Antimicrob Chemother 2020

MULTIRESISTENZ THERAPIE
Oritavancin

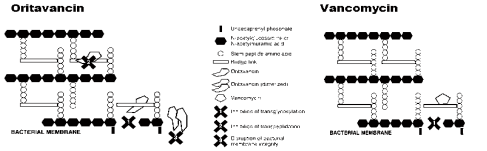
- **Dosierung Oritavancin**
  - LD 1.2 g Wo1 i.v.
  - ED 0.8 g ab Wo2 i.v.
- **CAVEAT's**
  - Infusionsdauer 3 Stunden
  - Interaktionen mit Heparin, Marcoumar & Gerinnungtests
- **Indikation**
  - MRGP-Spektrum inkl VRE
  - VRE-Infektionen



	antibiotic	breakpoint S	breakpoint R	susceptibility MIC_{50}	MIC_{90}	range
EUCAST	telavancin	≤ 0.125	> 0.125			~0.25
	oritavancin	≤ 0.125	> 0.125			~0.25
	oritavancin	≤ 0.125	> 0.125			~0.25
	ceftobiprole	≤ 2	> 2			-
	ceftaroline	≤ 1	> 1			~4
	linezolid	≤ 0.5	> 0.5			-
FDA	dalbavancin	≤ 0.25	≥ 1			~1

Boucher, N Engl J Med 2014 – Gilchrist, J Antimicrob Chemother 2015 – Thalhammer, Österreichische Ärztezeitung 2016
Tulkens, ECCMID 2018 – Schulz, Pharmacother 2018 – Chastain, Int J Antimicrob Agents 2019

MULTIRESISTENZ THERAPIE
Oritavancin



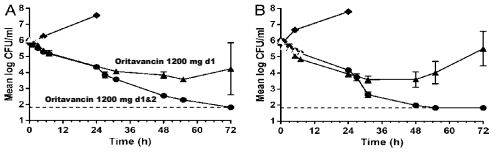
Inhibition of the transglycosylation (polymerization) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors.

Inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall.

Disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and rapid cell death.

Zhanel, Clin Infect Dis 2012 – Zeng, Spring Habor Perspect Med 2016

MULTIRESISTENZ THERAPIE
Oritavancin



DOSIERUNG

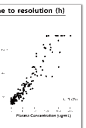
2 x 1200 mg Oritavancin innerhalb von 24 Stunden

Belley, Antimicrob Agents Chemother 2018

MULTIRESISTENZ THERAPIE
Oritavancin

MoA		Oritavancin	Dalbavancin
Inhibition of transpeptidation		+	–
Lipid II binding	Dimerization	+	–
	Membrane anchoring	+	+
Disruption of cell membrane integrity		+	–

Coagulation test	Maximum time to resolution (h)
Phospholipid dependent	
PT/INR	12
aPTT	120
ACT	24
SCT	18
DRVVT	72
APCR	Unaffected
Phospholipid independent	
Anti-factor Xa	Unaffected
TT	Unaffected
Anti-heparin-PF4	Unaffected
D dimer	72



- Lipoglykopeptidallergie
- Unfraktioniertes Heparin parenteral bis 48 Std nach Gabe von Oritavancin
- Interaktion mit Vit-K-Antagonisten
- Infusionsdauer 3 Std

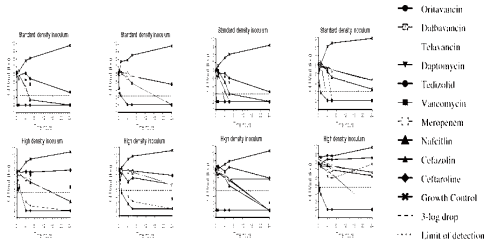
Contraindications	Dalbavancin	Oritavancin	Telavancin	Vancomycin
Known hypersensitivity to drug	N	N	N	N
Unfractionated heparin sodium therapy within 48 hours		N		

Boylan, Antimicrob Agents Chemother 2003 – Allen, FEMS Microbiology Rev 2003 – Seral, Antimicrob Agents Chemother 2003
Ambrose, Clin Infect Dis 2012 – Saravolatz, Clin Infect Dis 2015 – Cada, Hosp Pharma 2015 – Belley, Antimicrob Agents Chemother 2017

MULTIRESISTENZ THERAPIE
Die Betalaktamspieler

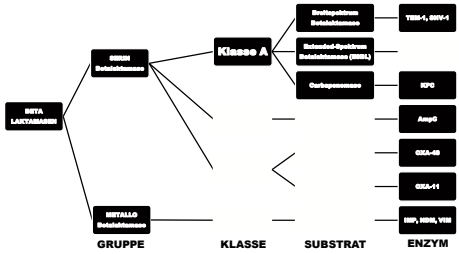
-
-
-
-
- Cefiderocol 3 x 2.0 g
-
- Ceftazidim/Avibactam 3 x 5.0 g
- Ceftolozan/Tazobactam 3 x 3.0 g
-
-
- Imipenem/Relebactam 3 x 1.5 g
-
- Meropenem/Vaborbactam 3 x 4.0 g
-
-

MULTIRESISTENZ THERAPIE
Oritavancin



Sweeney, Diagn Microbiol Infect Dis 2017

MULTIRESISTENZ THERAPIE
Amoxi/Clav & Ampi/Sulb



MULTIRESISTENZ THERAPIE
Cephalosporin plus Clavulansäure

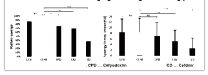
- **Cefixime plus Amoxi/Clav**
  - Aktivität gegen ESBL (CTX-M-15)
    - E. coli, Klebsiella spp.
  - KEINE Aktivität gegen AmpC
  - immer mikrobiolog Testung
- **Cefalexin plus Amoxi/Clav**
  - CDI-Risiko geringer, da Cefalexin nicht fäkal ausgeschieden
- **Amoxi/Clav plus**
  - Cefdinir, Cefpodoxim
  - Ceftibuten

Ceftibuten plus Amoxi/Clav

Organism	MIC, mg/ml	Amoxi/Clav 2:1 (mg/ml)	Ceftibuten (mg/ml)	Amoxi/Clav 2:1 (mg/ml)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Cefexim plus Clavulansäure

Cefixim 8 mg/kg KG 1x tgl – 2 x 0.4 (0.8) g p.o.
Amoxi/Clav 15 – 25 mg/kg KG 2x tgl – 2 x 1.5 g p.o.



Livermore, Int J Antimicrob Chemother 2011 – Bingen, Antimicrob Agents Chemother 2013 – Jubb, Achaogen 2017
Hawkey, J Antimicrob Chemother 2018 – Al-Tamimi, Microbiol Drug Res 2019

THERAPIE[START]

MULTIRESISTENZ THERAPIE
Cefto/Taz & Cefta/Avi

MULTIRESISTENZ THERAPIE
Cefoxitin

Pharmacological Study of Cefoxitin as an Alternative Antibiotic Therapy to Carbapenems in Treatment of Urinary Tract Infections Due to Extended-Spectrum-β-Lactamase-Producing *Escherichia coli*

Antibiotic susceptibility profiles of ESBL-EC strains, according to EUCAST breakpoints ($n = 145$)

Antibiotic class	No. (%) of susceptible strains
Third-generation cephalosporins	15 (10.3)
Fourth-generation cephalosporins	44 (30.3)
Imipenem	145 (100)
Amoxicillin-clavulanate	129 (88.9)
Piperacillin-tazobactam	140 (96.5)
Cefoxitin	(142 (97.9))
Gentamicin	95 (65.5)
Amikacin	141 (97.2)
Any aminoside	142 (97.9)
Ciprofloxacin	62 (42.7)
Trimethoprim-sulfamethoxazole	26 (17.9)

- Dosierung (max.) 3 x 4.0 g
- Aktivität
  - ESBL, Anaerobier
- Indikation: HWI, Pyelonephritis
- Nebenwirkung
  - Antikoagulantien & Blutungsgefahr

Dosage	Duration of infusion	% of strains with pharmacological success by target* T>MIC = 50%	T>MIC = 100%	T>4MIC = 50%	T>4MIC = 100%
2 g 4 times/day	1 h	92	23	70	3.5
2 g 4 times/day	4 h	100	76	99	38
6 g/day	Continuous	100	100	100	98.5

*The probability of target attainment was calculated with all strains susceptible to cefoxitin according to antibiotic susceptibility testing (n = 142).

Guet-Revillet, Antimicrob Agents Chemother 2014

MULTIRESISTENZ THERAPIE
Ceftazidim/Avibactam

Combinations of avibactam and carbapenems exhibit enhanced potencies against drug-resistant Mycobacterium abscessus.

AIM: The objective of this study was to assess if avibactam, a new β-lactamase inhibitor, can restore the potency of carbapenems, a subclass of β-lactams, against Mycobacterium abscessus clinical isolates

MATERIALS & METHODS: 28 M. abscessus clinical isolates that are resistant to multiple drugs currently used to treat this infection were included. MIC of carbapenems alone and in combinat on with avibactam against these strains were determined.

RESULTS: Tebipenem, an oral carbapenem, and ertapenem and panipenem exhibited the greatest shift in MIC when supplemented with avibactam.

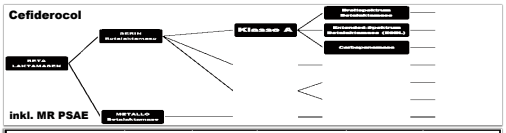
CONCLUSION: Avibactam restores MICs of tebipenem, ertapenem and panipenem against M. abscessus to therapeutically achievable concentrations and raises the possibility of usefulness of these carbapenems to treat drug-resistant M. abscessus infections.

In Vitro Discordance with In Vivo Activity: Humanized Exposures of Ceftazidime-Avibactam, Aztreonam, and Tigecycline Alone and in Combination against New Delhi Metallo-β-Lactamase-Producing Klebsiella pneumoniae in a Murine Lung Infection Model.

The management of infections with New Delhi Metallo-beta-lactamase-1 (NDM) producing bacteria remains clinically challenging given the multi-drug resistant (MDR) phenotype associated with these bacteria. Despite resistance in vitro, ceftazidime-avibactam previously demonstrated in vivo activity against NDM+ Enterobacteriaceae. Herein, we observed in vitro synergy with ceftazidime-avibactam and aztreonam against a MDR K. pneumoniae harboring NDM. In vivo, humanized doses of ceftazidime-avibactam monotherapy resulted in > 2 log_{10}CFU bacterial reduction, therefore, no in vivo synergy was observed.

Kaushik, Future Microbiol 2017 – Monogue, Antimicrob Agents Chemother 2017

MULTIRESISTENZ THERAPIE
Cefiderocol

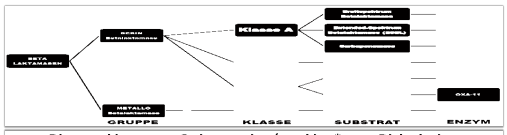


CEF-TAZ	+				+
MER-VAR	+	+			-
IMI-REL	+	+			+
CAZ-AVI	+	+	+	**	+
AZT-AVI	+	+	+	+	
SUL-DUR	+	+	+	+1	
FEP-TAN	+	+	+	±	±
CFDC	+	+	+	±	±

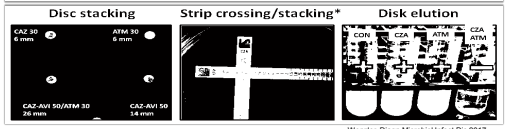
[1]Angabe widerspricht publizierten in vitro Daten; Substanz zielt auf A. baumanii Infektionen
*In vitro wirksam, klinische Wirksamkeit nicht belegt
**In-label Kombination CAZ-AVI + AZT in vitro und klinisch wirksam

Paterson, Curr Opin Infect 2020

MULTIRESISTENZ THERAPIE
Aztreonam/Avibactam



Disc stacking | Strip crossing/stacking* | Disk elution



Wenzler, Diagn Microbiol Infect Dis 2017

MULTIRESISTENZ THERAPIE
Cefiderocol

Cefiderocol resistance and NDM resistance mechanism?

- 48,7% of NDM producers resistant against cefiderocol (18 out of 37)
- 66,7% of cefiderocol resistant isolates NDM producers

Whole Genome Sequencing:

- Combination of 2 resistance mechanisms
- NDM & OXA: 48,1% (18 out of 27)
- NDM/OXA & CTX-M-15: 22% (6 out of 27)

Conclusion:

- low resistance rate of 7.7% also in comparison to other antibiotics
- Cefiderocol could be a promising antibiotic agent for the treatment of multidrug resistant gram negative bacteria

RESISTANT ISOLATES WITH RESISTANCE MECHANISM	NUMBER OF RESISTANT ISOLATES
Klebsiella pneumoniae	6
ESBL	-
CTX-M	-
KPC	-
NDM	5
OXA-48	-
Escherichia coli	5
CTX-M1	-
NDM	4
NDM&OXA48	-
Enterobacter cloacae	5
NDM	4
VIM	-
Acinetobacter baumannii	4
OXA	-
NDM	1
Citrobacter freundii	-
VIM	-
Klebsiella oxytoca	-
NDM	-
Serratia marcescens	-
NDM	-
Resistant isolates in total	27

MEDIZINISCHE UNIVERSITÄT WIEN

Cefiderocol antimicrobial susceptibility against multidrug resistant Gram-negative bacteria in a tertiary care hospital
Medical University of Vienna, Department of Laboratory Medicine, Division of Clinical Microbiology, Vienna, Austria

Ludwig, Urologe 2022

MULTIRESISTENZ THERAPIE
Lücken beachten

- **Cefiderocol**
- **Ceftazidim/Avibactam**
- **Ceftolozan/Tazobactam**
- **Aztreonam/Avibactam**

KEINE AUSREICHENDE AKTIVITÄT GEGEN STAPHYLKOKOKKEN & STREPTOKOKKEN

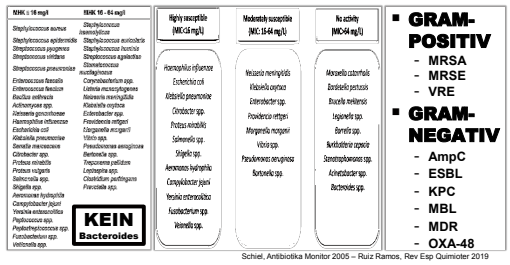
MULTIRESISTENZ THERAPIE
Ertapenem – Meropenem

Double-carbapenem therapy in the treatment of multidrug resistant Gram-negative bacterial infections: a systematic review and meta-analysis

- **Ertapenem**
  - Affinität zu KPC
  - Reduktion der Carbapenemasen
- **Doripenem, Meropenem**
  - geringere Hydrolyse
  - höhere Konzentration
  - bessere Keimabtötung

Li, BMC Infect Dis 2020

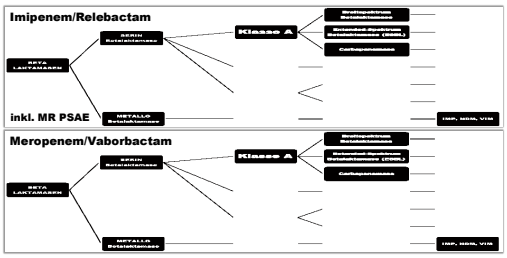
MULTIRESISTENZ THERAPIE
Fosfomycin



- **GRAM-POSITIV**
  - MRSA
  - MRSE
  - VRE
- **GRAM-NEGATIV**
  - AmpC
  - ESBL
  - KPC
  - MBL
  - MDR
  - OXA-48

Schiel, Antibiotika Monitor 2005 – Ruiz Ramos, Rev Esp Quimioter 2019

MULTIRESISTENZ THERAPIE
Imi/Relebactam – Mero/Vaborbactam



MULTIRESISTENZ THERAPIE
Fosfomycin

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

Background. We aimed to determine whether daptomycin plus fosfomycin provides higher treatment success than daptomycin alone for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and endocarditis.

Methods. A randomized (1:1) phase 3 superiority, open-label, and parallel group clinical trial of adult inpatients with MRSA bacteremia was conducted at 18 Spanish hospitals. Patients were randomly assigned to receive either 10 mg/kg of daptomycin intravenously daily plus 2 g of fosfomycin intravenously every 6 hours, or 10 mg/kg of daptomycin intravenously daily. Primary endpoint was treatment success 6 weeks after the end of therapy.

Results. Of 167 patients randomized, 155 completed the trial and were assessed for the primary endpoint. Treatment success at 6 weeks after the end of therapy was achieved in 40 of 74 patients who received daptomycin plus fosfomycin and in 34 of 81 patients who were given daptomycin alone (54.1% vs 42.0%; relative risk, 1.29 [95% confidence interval, .93–1.8]; $P = .135$). At 6 weeks, daptomycin plus fosfomycin was associated with lower microbiologic failure (0 vs 9 patients; $P = .003$) and lower complicated bacteremia (16.2% vs 32.1%; $P = .022$). Adverse events leading to treatment discontinuation occurred in 13 of 74 patients (17.6%) receiving daptomycin plus fosfomycin, and in 4 of 81 patients (4.9%) receiving daptomycin alone ($P = .018$).

Conclusions. Daptomycin plus fosfomycin provided 12% higher rate of treatment success than daptomycin alone, but this difference did not reach statistical significance. This antibiotic combination prevented microbiological failure and complicated bacteremia, but it was more often associated with adverse events.

Pujol, Clin Infect Dis 2020

MULTIRESISTENZ THERAPIE
Fosfomycin

Antibiogramm	Keim 1	Keim 2
Penicillin-G		+
Piperacillin	-	
Piperacillin/ Tazobactam	+	
Cefepim	-	
Ceftazidim	-	
Ceftazidim/ Avibactam	+/- [8]	
Ceftolozan/ Tazobactam	+ [1]	
Imipenem	-	
Meropenem		

Antibiogramm	Keim 1	Keim 2
Aztreonam	-	
Ciprofloxacin	+/-	
Amikacin	+	
Tobramycin	+	
Vancomycin		+
Clindamycin		-
Colistin	+ [2]	
Fosfomycin	- [1024]	
Linezolid		+

+ = sensibel, +/- = intermediär*, - = resistent, N = nicht indiziert, [ ] minimale Hemmkonzentration in mg/l
* Bitte beachten. Gemäß EUCAST ist die Kategorie intermediär (±) neu zu interpretieren. Bitte berücksichtigen Sie daher bei der Antibiotikaauswahl, dass bei Verwendung eines Antibiotikums, dass mit ± klassifiziert wurde, die Wahrscheinlichkeit eines therapeutischen Erfolgs hoch ist, wenn der Infektionserreger einer höheren oder intensiveren Antibiotikawirkung ausgesetzt wird.

Zusätzliche Bemerkung zu Keimnr.
1) Colistin+Daptomycin MHK: 3, in vitro kein Synergieeffekt beobachtbar.
Ceftolozan/Tazobactam+Fosfomycin MHK: 0.38, in vitro Synergismus beobachtbar.
Ceftazidim/Avibactam+Fosfomycin MHK: 4; in vitro kein Synergieeffekt beobachtbar.

Imipenem/Relebactam MHK: 3 mg/L (R)

AKH Wien 2020

MULTIRESISTENZ THERAPIE
Fosfomycin

Evaluation of synergistic activity of fosfomycin in combination with novel ß-lactams/ß-lactamase inhibitor combinations (βL-βLICs) against KPC-producing *Klebsiella pneumoniae* clinical isolates

	SYN	ADD	gesamt	MHK_{Abfall}
CAZ/AVI	22.7%	45.5%	68.2%	2.36-fach
MER/VAB	31.8%	36.4%	68.2%	7.46-fach
IMI/REL	13.6%	63.6%	77.2%	4.87-fach
CEF/TAZ	0%	22.7%	22.7%	2.00-fach

Gaibani, Int J Antimicrob Agents 2022

MULTIRESISTENZ THERAPIE
Fosfomycin

Ceftazidime-avibactam, meropenen-vaborbactam, and imipenem-relebactam in combination with aztreonam against multidrug-resistant, metallo-β-lactamase-producing *Klebsiella pneumoniae*

The spread of multidrug-resistant (MDR), metallo-β-lactamase (MBL)-producing *Klebsiella pneumoniae* represents a major therapeutic challenge. The newly introduced β-lactam-β-lactamase inhibitors (βLBLIs), ceftazidime avibactam (CAZ-AVI), meropenem vaborbactam (MVV), and imipenem relebactam (I-R) are inactive against MBLs. The aim of this study was to evaluate the in vitro efficacy of aztreonam (ATM) in combination with CAZ-AVI, MVV, and I-R against 40 MDR, MBL-producing, and serine-β-lactamases co-producing *Klebsiella pneumoniae* using the Etest method. Synergy was defined as a fractional inhibitory concentration index ≤0.5. All isolates were resistant to ATM, CAZ-AVI, and I-R and 38/40 (95%) were resistant to MVV. Synergy was observed in 97.5% in the combinations CAZ-AVI-ATM, and I-R-ATM and in 72.5% in the combination MVV-ATM. Further clinical studies are required to confirm the efficacy of these antimicrobial combinations.

- **FOSFOMYCIN plus**
  - **Ceftazidim/Avibactam**
  - **Imipenem/Relebactam**
  - **Meropenem/Vaborbactam**

- **Synergismus**
  - **97.5% CAZ/AVI-ATM**
  - **97.5% I/R-ATM**
  - **72.5% M/V-ATM**

Maraki, Eur J Clin Microbiol Infect Dis 2021

MULTIRESISTENZ THERAPIE
Delafloxacin

Clinical Infectious Diseases
INVITED ARTICLE
REVIEWS OF ANTI-INFECTIVE AGENTS: Jason D. Sarvolatz, Section Editor

Delafloxacin: A New Anti–methicillin-resistant *Staphylococcus aureus* Fluoroquinolone

Lewis B. Sorensen[1] and Gary E. Stein[2]

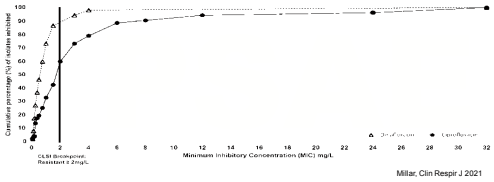
Estimated Glomerular Filtration Rate (eGFR)(mL/min/1.73m²)	Recommended Dosage Regimen for BAXDELA	
	Oral	Intravenous
30-89	No dosage adjustment	No dosage adjustment
15-29	No dosage adjustment	200 mg every 12 hours
End Stage Renal Disease (ESRD)(≥15 including hemodialysis)	Not Recommended	

- **parenteral**
  - **300 mg 2x tgl über 60 min**
- **oral**
  - **450 mg 2x tgl**

Saravolatz, Clin Infect Dis 2019

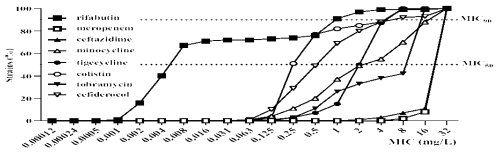
MULTIRESISTENZ THERAPIE
Delafloxacin

Ciprofloxacin	Ciprofloxacin MIC (mg/L) Mean ± SEM	Delafloxacin MIC (mg/L) Mean ± SEM [Paired with Ciprofloxacin comparator]	p value
Total (isolates n = 50)	3.20 ± 0.58	1.13 ± 0.16	0.0001***
Sensitive [S ≤ 0.5 mg/L] (n = 10)	0.27 ± 0.04	0.17 ± 0.02	0.011**
Intermediate [I = 1-4 mg/L] (n = 13)	1.15 ± 0.30	0.78 ± 0.13	0.011**
Resistant [R ≥ 8.0 mg/L] (n = 26)	4.89 ± 0.88	1.28 ± 0.21	0.001***
Hypothetical Strain (MIC = 128.0)	0.19	0.75	



Millar, Clin Respir J 2021

MULTIRESISTENZ THERAPIE
Rifabutin



CPR-Acinetobacter baumanii

Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	EUCAST %S	EUCAST %R	CLSI %S	CLSI %I	CLSI %R
Rifabutin	0.008	1	–	–	–	–	–
Meropenem	>32	>32	0	100.0	0	0.3	99.7
Ceftazidime	>32	>32	–	–	6.8	4.5	88.7
Minocycline	4	32	–	–	55.3	14.7	30.0
Tigecycline	2	8	–	–	–	–	–
Colistin	0.25	8	84.6	15.4	84.6	–	15.4
Tobramycin	>16	>16	38.2	61.8	38.2	3.4	58.4
Cefiderocol	1	8	–	–	87.7	4.6	7.8

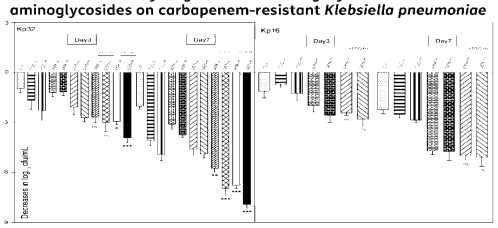
Trebosc, J Antimicrob Chemother 2020

MULTIRESISTENZ THERAPIE
Pseudomonas aeruginosa

ALTE OPTIONEN	NEUE OPTIONEN
Amikacin	**Cefiderocol**
Aztreonam	**Ceftazidim/Avibactam**
Cefepim	**Ceftolozan/Tazobactam**
Ceftazidim	**(Delafloxacin)**
	Imipenem/Relebactam
Colistin	**Meropenem/Vaborbactam**
Imipenem	
Meropenem	
Piperacillin/Tazobactam	
Tobramycin	

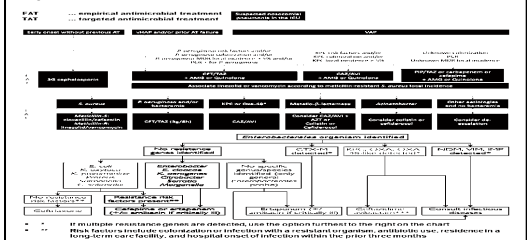
MULTIRESISTENZ THERAPIE
Tigecyclin

In vitro* and *in vivo* synergistic effects of tigecycline combined with aminoglycosides on carbapenem-resistant *Klebsiella pneumoniae



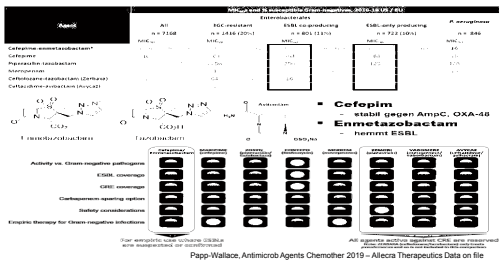
Ni, J Antimicrob Chemother 2021

MULTIRESISTENZ THERAPIE
Fokusabhängige Antibiotikaauswahl



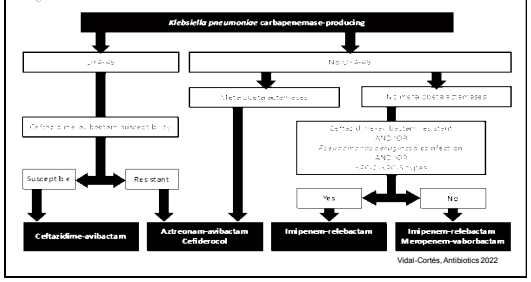
Zaragoza, Crit Care 2020 – Wu, Mayo Clin Proc 2020

MULTIRESISTENZ THERAPIE
Cefepim/Enmetazobactam



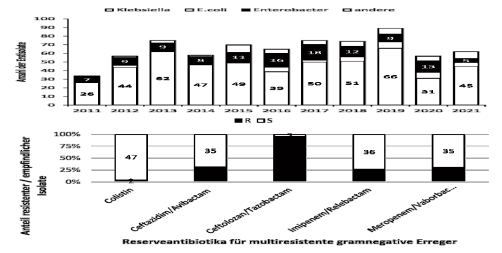
Papp-Wallace, Antimicrob Agents Chemother 2019 – Allecra Therapeutics Data on file

MULTIRESISTENZ THERAPIE
Enterobakterien (MRGN)



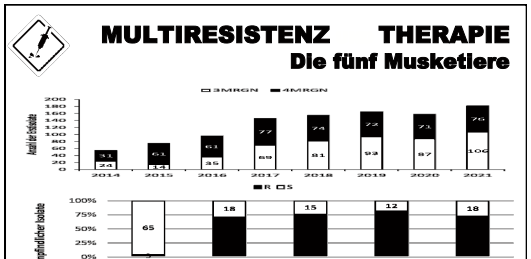
Vidal-Cortés, Antibiotics 2022

MULTIRESISTENZ THERAPIE
Die fünf Musketiere



Resistenzbericht MUI 2022

MULTIRESISTENZ THERAPIE
Die fünf Musketiere



Resistenzbericht MUI 2022

ICU ADVANCED
LUNGE UND BAUCH

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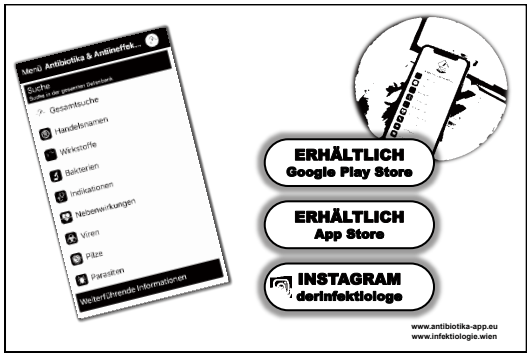
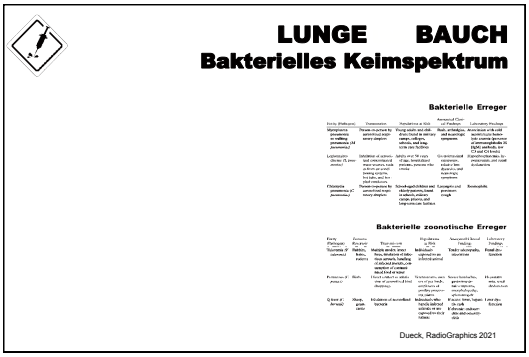
https://www.istockphoto.com/de/search/2/image?phrase=%22Hand%20Gesti%20Thumbs%20up%20Image%20Illustration%22 / 05/12/2021 14:10



LUNGE BAUCH
Bakterielles Keimspektrum



Dueck, RadioGraphics 2021

LUNGE BAUCH
Haemophilus Influenzae

- **CAPNETZ 2004 ► 2016**
  - S. pneumoniae 58.0% ► 37.5%
  - H. influenzae 12.2% ► 20.8%

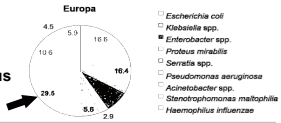
	H. influenzae (n = 30)	S. pneumoniae (n = 30)	P
Shock	0	13.9	.03
Admission to ICU	15.2	16.7	.9
PORT score	92 (81–118)	100.5 (86–130.75)	.7
Pneumonia Severity Index	4 (3–4)	4 (3–4)	1
ATS/IDSA severe pneumonia	18.2	16.7	.9
eSOFA ≥ 2	3	13.9	.1
In-hospital mortality	0	11.1	.05
30-d mortality	0	13.9	.03

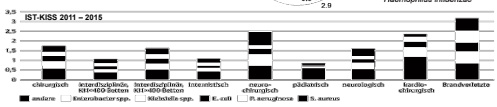
- **EUCAST 2018**
  - Makrolide im Antibiogramm wegen unzureichender Aktivität nicht angeben

Shoar, Open Forum Infect Dis 2021 – Braeken, Infection 2021

LUNGE BAUCH
Keimspektrum & Pat*Innen-Kollektiv

- Mikrobiom bzw. Resistenzlage abhängig von
  - Ländern
  - Regionen
  - Krankenhäusern
  - ICU's im selben KH-Haus



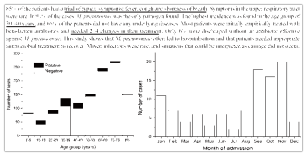


Sader, Int J Antimicrobiol Agents. 2014 – Dalhoff, Pneumologie 2018

LUNGE BAUCH
Mycoplasma pneumoniae

Macrolide-Resistant *Mycoplasma pneumoniae* Infections in Children, Ohio, USA

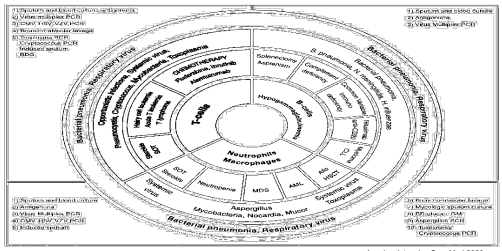
- protrahierter Verlauf
- höhere Morbidität
- Makrolidresistenzen
  - 88.3% China
  - 49.4% – 83.3% Japan
  - 70.3% Korea
  - 20.0% Italien
  - 3.1% Deutschland
  - 2.8% – 10.0% USA
  - 3.1% Deutschland



Emergence of Macrolide-Resistant *Mycoplasma pneumoniae* during an Outbreak in a Primary School

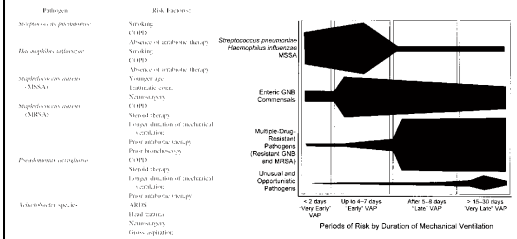
Lanata, Emerg Infect Dis 2021 – Ishimaru, Intern Emerg Med 2021 – Hubert, Pathogens 2021

LUNGE BAUCH
Immunsuppression & Infektion



Azoulay, Intensive Care Med 2020

LUNGE BAUCH
Beatmung & Erregerspektrum



Park, Resp Care 2005

LUNGE BAUCH
Acinetobacter baumannii

- **Acinetobacter species**
  - A. baumannii, A. nosocomialis, A. pittii
- **Inzidenz**
  - zunehmend
  - regional unterschiedlich
  - KH-Ausbrüche möglich
- **Resistenz**
  - intrinsisch: Penicillinen, Cephalosporinen
  - erworben: Chinolone, Aminoglykosid
  - Carbapeneme
    - Oxacillinasen (OXA-23, OXA-72, OXA-58-like)
    - Metallobetalaktamasen (NDM, VIM)
  - Panresistenz

Dalhoff, AWMF S3-LL Nosokomiale Pneumonie 2017

LUNGE BAUCH
MRSA-Screening

Background: Many trauma centers have empiric treatment algorithms for ventilator-associated pneumonia (VAP) treatment prior to culture results that include antibiotic agents for methicillin-resistant *Staphylococcus aureus* (MRSA) coverage that can have adverse effects. This is the only study to evaluate risk factors and MRSA nasal swabs to risk-stratify trauma patients for MRSA VAP, thereby potentially limiting the need for empiric vancomycin.
Patients and Methods: This was a single institution retrospective cohort study. Adult patients admitted to the trauma intensive care unit (ICU) between January 2013 and December 2017 who had a MRSA nasal swab and subsequently met criteria for VAP were included. Demographics, risk factors for MRSA pneumonia, and culture results were collected.
Results: A total of 140 patients met inclusion criteria. The negative predictive value (NPV) of MRSA nasal swab at predicting subsequent MRSA pneumonia was 97%. The sensitivity, specificity, and positive predictive value were 50.0%, 96.2%, and 44.4%, respectively. Smokers were more likely to develop MRSA pneumonia, odds ratio: 7.0 (p=0.02). When considering non-smokers with a negative MRSA nasal swab, NPV was 100%.
Conclusions: This is the only study to date that assesses the utility of MRSA nasal swab and risk factor data to guide empiric VAP antibiotic therapy in trauma patients. Smoking was found to be a risk factor for MRSA pneumonia. The use of MRSA nasal swabs in combination with smoking status to guide empiric use of MRSA coverage antibiotic agents is recommended because of a 100% NPV. When utilized, as many as 68% of patients may safely be spared MRSA coverage antibiotic agents and the related adverse effects.

- **Risikofaktor Rauchen**
- **MRSA-Screening (nasal)**
- **NPV 100%**
- **Surveillance**

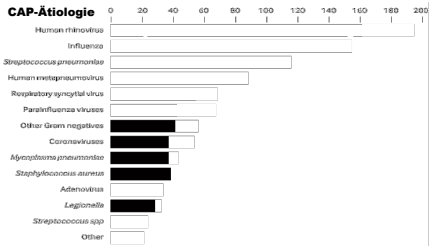
Stodghill, Surg Infect 2021

LUNGE BAUCH
Stenotrophomonas maltophilia

- **Klinik**
  - meist Kolonisation bei beatmeten Pat*innen
  - late-onset VAP
  - selten schwere Pneumonie
- **Risikofaktoren**
  - antimikrobielle Breitspektrumtherapie
  - Carbapeneme
- **umfangreiche intrinsische Resistenz**
- **Therapieoptionen**
  - Cotrimoxazol (Mittel der Wahl)
  - Fluorchinolone

Dalhoff, AWMF S3-LL Nosokomiale Pneumonie 2017

LUNGE BAUCH
Virus vs Bakterien



Welte, Med Klinik 2006 – Maskell, Am J Respir Crit Care Med 2006 – Jain, N Engl J Med 2015 – Ewig, Pneumologie 2016
Wunderink, BMJ 2017

LUNGE BAUCH
Virale Erreger

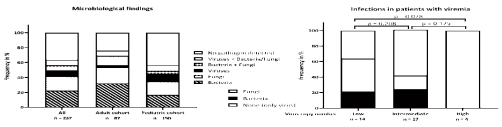
Virus	Structure	Reservoir	Transmission	Populations at Risk
Influenza	Enveloped segmented negative-sense ssRNA, with helical capsid	Humans, pigs	Direct contact or inhalation of infected respiratory droplets	Elderly and immunocompromised patients, solid organ transplant recipients, pregnant women
Parainfluenza	Enveloped negative-sense ssRNA, with helical capsid	Humans	Direct contact or inhalation of infected respiratory droplets	Young children; elderly and immunocompromised patients, particularly lung and hematopoietic cell transplant recipients
RSV	Enveloped negative-sense ssRNA, with helical capsid	Humans	Direct contact or inhalation of infected respiratory droplets	Premature infants or children with congenital heart disease, chronic lung disease, or multiple or congenital abnormalities or who are immunocompromised
Adenovirus	Nonenveloped linear dsDNA	Humans	Direct contact or inhalation of infected respiratory droplets	Immunocompromised patients, persons in military camps or exposed to contaminated swimming pools
HMPV	Enveloped negative-sense ssRNA	Humans	Direct contact or inhalation of infected respiratory droplets	Young children and infants, prematurity

Dueck, RadioGraphics 2021

LUNGE BAUCH
Virus vs Bakterien

Viremia was documented in 36 (15 %) episodes investigated, including the detection of HHV6 (n=14), EBV (n=15), CMV (n=6), or HAdV (n=1). While low or intermediate levels of viremia (<10⁴ virus copies/ml) were commonly associated with bacterial or fungal co-infection, viremia at higher levels (>10⁴ copies/ml) was documented in patients without evidence for other infections, raising the possibility that at least in some instances the onset of fever may have been attributable to the virus detected.

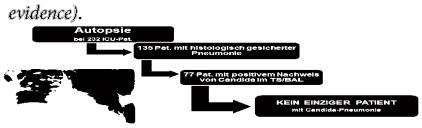
The observations suggest that viral infections, potentially resulting from reactivation, might also play a clinically relevant role in patients receiving chemotherapy for treatment of malignant neoplasms, and routine screening for viremia in this clinical setting might be warranted.



Obrová, Am J Hematol 2021

LUNGE BAUCH
Candida & Respirationstrakt

58. Growth of *Candida* from respiratory secretions usually indicates colonization and rarely requires treatment with antifungal therapy *(strong recommendation; moderate-quality evidence)*.



Autopsiestudie zur Evaluierung der Candida-Pneumonie über einen 2-jährigen Zeitraum

Meersseman, Intensive Care Med 2009 – Pappas, Clin Infect Dis 2016

LUNGE BAUCH
Aspergillose

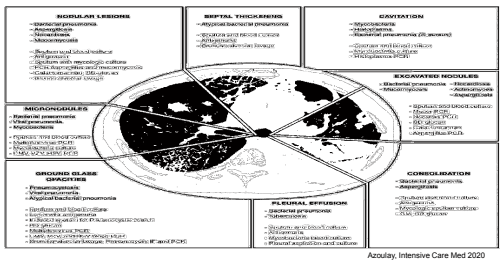
RISIKOPATIENT*INNEN

- angeborene Immundefekte
- lang anhaltende (> 10 Tage) Granulozytopenie
- allogene Stammzelltransplantation
- medikamentöse Immunsuppression
- Intensivpatienten
  - putative invasive pulm Aspergillose
- strukturelle Lungenerkrankung
  - chron pulm Aspergillose
  - COPD (BULPA-Kriterien)
- Influenzapneumonie

LUNGE BAUCH
"Spuckerling"

- **Tracheal- und Endobronchialsekret**
  - leichter zu gewinnen
  - hohe Kolonisationsrate im oberen Respirationstrakt
  - Pneumoniehäufigkeit wird überschätzt
  - NPV gut ►neg Proben ►keine Erreger wahrscheinlich
    - ABT für 48 – 72 Std unverändert
- **Bronchiallavage (BAL) und geschützte Bürste**
  - falsch-negative Ergebnisse häufiger
  - Entnahme vor AB-Wechsel noch wichtiger

LUNGE BAUCH
CT & Ätiologie

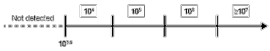


Azoulay, Intensive Care Med 2020

LUNGE BAUCH
Multiplex-PCR

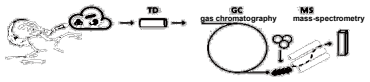
Multiplex PCR Panel	Type of Sample and Time to Results	Performance	Pathogens/Markers of Resistance Genes Detected
BioFire® FilmArray® Pneumonia Panel and Pneumonia Panel Plus (bioMérieux SA, France)	BAL/mini-BAL, tracheal aspirate, induced and expectorated sputum Time to results: 1 h	Both panels: BAL/BAL-like: Sens/Spec= 96.2%/98.3% Sputum: Sens/Spec= 96.3%/97.2%	VIRALES: • Adenovirus • Coronavirus • Human Metapneumovirus • Human Rhinovirus/Enterovirus • Influenza A • Influenza B • Parainfluenza Virus • Respiratory Syncytial Virus; ANTIMICROBIAL RESISTANCE GENES: Methicillin resistance: • mecA/C and MRSA; Carbapenemases: • KPC • NDM • OXA-48-like • VIM • IMP; ESBL: • CTX-M; BACTERIAL: Gram Positive Bacteria: • Acinetobacter calcoaceticus-baumannii complex • Enterococcus faecalis/E. faecium • Enterobacter cloacae complex • Escherichia coli • Klebsiella pneumoniae group • Klebsiella oxytoca • Proteus spp. • Pseudomonas aeruginosa • Serratia marcescens • Haemophilus spp. • Pseudomonas aeruginosa • Streptococcus agalactiae • Streptococcus pneumoniae • Streptococcus pyogenes • Staphylococcus aureus; ATYPICAL BACTERIAL: Obligate Bacteria: • Chlamydophila pneumoniae • Legionella pneumophila • Mycoplasma pneumoniae

Values reported by the BioFire Pneumonia Panel



Xu, Microorganisms 2021

LUNGE BAUCH
BreathDx – Atemtest



Molecular Analysis of Exhaled Breath as Diagnostic Test for VAP

- Sens 98%
- Spez 49%
- NPV 96%

GC-MS-1	Culture positive	Culture negative	Total
Breath positive	43	25	68
Breath negative	1	24	25
Total	44	49	93

GC-MS-2	Culture positive	Culture negative	Total
Breath positive	44	24	68
Breath negative	1	20	21
Total	45	44	89

Oort, BMC Pulm Med 2017 – Oort, Thorax 2021

LUNGE BAUCH
Interpretiere die Befunde richtig

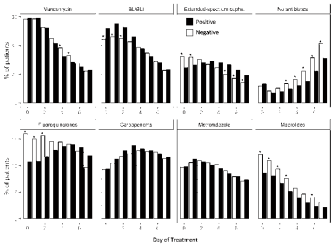
DIE PILZDIAGNOSTIK IST

Candida	Gerät II-Verfahren	[illegible] Hefeähnlich, indirekt [illegible]	mykologische Standardkultur Hefen	Nachweis der Hefehyphen [illegible]	+	-	HE-Färbung mit [illegible]	Nachweis pseudomembranöser [illegible]	abdominelle Infektionen [illegible] Sepsis der Neu-MG
Aspergillus	Gerät II-Verfahren	keine sichere [illegible]	mykologische Standardkultur	[illegible]	+	+	HE-Färbung mit [illegible]	[illegible]	Bronchoskopie [illegible]
Mucorales	Gerät II-Verfahren	[illegible]	mykologische Standardkultur				keine sichere [illegible]	keine standardisierte [illegible]	Bronchoskopie [illegible]
Fusarium	Gerät II-Verfahren	[illegible]	mykologische Standardkultur Hefen		+	(+)	keine spezifische [illegible]	keine standardisierte [illegible]	Bronchoskopie [illegible]

IST AUFWENDIG UND NICHT IMMER BEWEISEND

Lilienfeld-Toal, Dtsch Ärztebl Int 2019

LUNGE BAUCH
Kultur aus dem Respirationstrakt



- **… demonstrated little substantive differences between patients with positive and negative cultures**
- **… suggesting that results of respiratory cultures were not a strong influence on antibiotic treatment decisions**

Taissa, Infect Control Hosp Epidemiol 2021

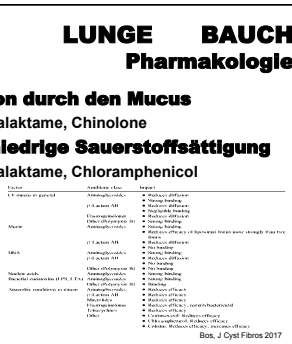
LUNGE BAUCH
Pharmakologie

- **divalente Kationen**
  - reduzieren Chinolon-Aktivität
- **anaerobes Milieu**
  - beeinflusst Wirksamkeit von Aminoglykosiden
- **saurer pH-Wert und Eiter**
  - inaktiviert Aminoglykoside und Makrolide
- **Inokulum**
  - in VAP (-10^9) grösser als in der in-vitro Testung (10^5 – 10^6)
- **reduzierte Diffusion durch Mucus**
  - Aminoglykoside, Betalaktame, Chinolone
- **reduzierte Aktivität bei niedriger Sauerstoffsättigung**
  - Aminoglykoside, Betalaktame, Chloramphenicol
- **Alginat wichtiger Resistenzfaktor**

Bergogne-Berezin, Pulm Pharm 1995 – Bos, J Cyst Fibros 2017

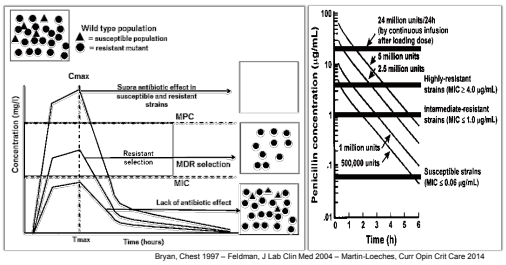
LUNGE BAUCH
Pharmakologie

- **reduzierte Diffusion durch den Mucus**
  - Aminoglykoside, Betalaktame, Chinolone
- **red Aktivität bei niedrige Sauerstoffsättigung**
  - Aminoglykoside, Betalaktame, Chloramphenicol
- **Inaktivierung d Moleküle**
  - Aminoglykoside
- **Alginat wichtiger Resistenzfaktor**



Bos, J Cyst Fibros 2017

LUNGE BAUCH
Pharmakologie



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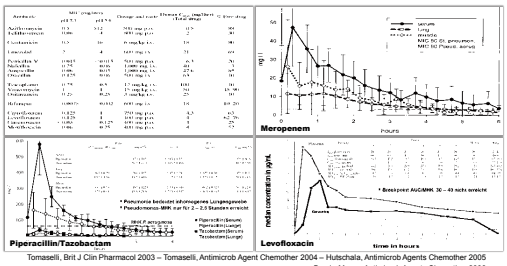
LUNGE BAUCH
Pharmakologie



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Barcia-Macay, Antimicrob Agents Chemother 2006

LUNGE BAUCH
VAP-Therapieoptionen

- **MRSA-Therapie**
  - wenn > 10 – 20% der *S. aureus*-Stämme MR-pos
- **PSAE-Zweifachtherapie**
  - wenn Resistenzrate >10%

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam-Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam-Based Agents
Glycopeptides **Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)**	**Antipseudomonal penicillins** **Piperacillin-tazobactam 4.5 g IV q8h**	**Fluoroquinolones** **Ciprofloxacin 400 mg IV q8h** **Levofloxacin 750 mg IV q24h**
OR	OR	OR
Oxazolidinones **Linezolid 600 mg IV q12h**	**Cephalosporins** **Cefepime 2 g IV q8h** **Ceftazidime 2 g IV q8h**	**Aminoglycosides** **Amikacin 15–20 mg/kg IV q24h** **Gentamicin 5–7 mg/kg IV q24h** **Tobramycin 5–7 mg/kg IV q24h**
	OR	OR
	Carbapenems **Imipenem 500 mg IV q8h** **Meropenem 1 g IV q8h**	**Polymyxins** **Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose)** **Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses**
	OR	
	Monobactams **Aztreonam 2 g IV q8h**	

Klompas, Clin Infect Dis 2017

LUNGE BAUCH
Therapieziel

Patient mit ambulanter erworbener Pneumonie

Gruppe 1a → Kuratives Therapieziel

Gruppe 1b → Kuratives Therapieziel

Gruppe 2 → Palliatives Therapieziel

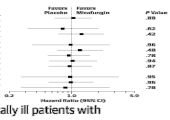
Die Prüfung des Therapieziels ist in vielen Fällen ein Prozess!

Ewig, Pneumologie 2021

LUNGE BAUCH
Empirische ICU-Candida-Therapie?

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure
The EMPIRICUS Randomized Clinical Trial

	Micafungin: Survived at Day 28, No.	Micafungin: Total No.	Placebo: Survived at Day 28, No.	Placebo: Total No.	Hazard Ratio (95% CI)
All patients	90	128	94	123	1.04 (0.84–1.67)
SOFA score					
<9	53	86	58	88	0.79 (0.32–1.96)
≥9	37	42	26	35	1.26 (0.73–2.27)
Admission category					
Surgical	23	34	23	31	0.97 (0.38–2.63)
Medical	67	94	63	92	1.23 (0.85–2.22)
Colonization index ≥0.5[a]	54	76	56	80	1.02 (0.58–1.80)
Corrected colonization index ≥0.4[b]	54	76	56	80	1.02 (0.58–1.80)
Candida score ≥3	66	96	58	85	0.85 (0.55–1.67)
(1→3)-β-D-glucan, pg/mL[c]					
<80	14	21	17	25	0.96 (0.27–3.33)
>80	61	91	59	84	0.98 (0.55–1.75)
>80	29	37	28	39	0.98 (0.27–2.69)



CONCLUSIONS AND RELEVANCE Among nonneutropenic critically ill patients with ICU-acquired sepsis, *Candida* species colonization at multiple sites, and multiple organ failure, empirical treatment with micafungin, compared with placebo, did not increase fungal infection-free survival at day 28.

Timsit, JAMA 2016

LUNGE BAUCH
Kurzzeittherapie

Ultra-Short-Course Antibiotics for Patients With Suspected Ventilator-Associated Pneumonia but Minimal and Stable Ventilator Settings

Background. Many patients started on antibiotics for possible ventilator-associated pneumonia (VAP) do not have pneumonia. Patients with minimal and stable ventilator settings may be suitable candidates for early antibiotic discontinuation. We compared outcomes among patients with suspected VAP but minimal and stable ventilator settings treated with 1–3 days vs >3 days of antibiotics.

Methods. We identified consecutive adult patients started on antibiotics for possible VAP with daily minimum positive end-expiratory pressure of ≤5 cm H_2O and fraction of inspired oxygen ≤40% for at least 3 days within a large tertiary care hospital between 2006 and 2014. We compared time to extubation alive vs ventilator death and time to hospital discharge alive vs hospital death using competing risks models among patients prescribed 1–3 days vs >3 days of antibiotics. All models were adjusted for patient demographics, comorbidities, severity of illness, clinical signs of infection, and pathogens.

Results. There were 1290 eligible patients, 259 treated for 1–3 days and 1031 treated for >3 days. The 2 groups had similar demographics, comorbidities, and clinical signs. There were no significant differences between groups in time to extubation alive (hazard ratio [HR], 1.16 for short- vs long-course treatment; 95% confidence interval [CI], .98–1.36), ventilator death (HR, 0.82 [95% CI, .55–1.22]), time to hospital discharge alive (HR, 1.07 [95% CI, .91–1.26]), or hospital death (HR, 0.99 [95% CI, .75–1.31]).

Conclusions. Very short antibiotic courses (1–3 days) were associated with outcomes similar to longer courses (>3 days) in patients with suspected VAP but minimal and stable ventilator settings. Assessing serial ventilator settings may help clinicians identify candidates for early antibiotic discontinuation.

Klompas, Clin Infect Dis 2017

LUNGE BAUCH
Dosierung inhalativer Antibiotika

Wirkstoff	Name	Inhalt/Ampulle bzw. Kapsel	Lösungsmittel/Ampulle	Dosierung/Tag	Inhalationsgeräte
Aztreonam	Cayston®	75 mg	1 ml	3 mal 75 mg	eflow® Akona®
Ceftazidim[b]		1 g			eflow® rapid PARI BOY® SX Kompressor - LC Sprint Vernebler
Colistin	Colistin-Kronos®	1 Mio. I.E.	2 ml	2 mal 1 Mio. I.E.	eflow® rapid PARI BOY® SX Kompressor - LC Sprint Vernebler; für Colistin Kronos® alternativ Akita® Jet
	ColiFin	1 oder 2 Mio. I.E.	4 ml	2 mal 1 - 3 Mio. I.E.	
	Bedim®	1 Mio. I.E.[c]	1 ml	2 mal 1 - 2 Mio. I.E.	I Neb.®
	Colobreathe®	1.662.500 I.E. 125 mg		2 mal 1 Kapsel	Trockenpulverinhalator
Gentamicin[b]	Refobacin	80 oder 120 mg	2 ml	2 mal 80 - 120 mg	eflow® rapid PARI BOY® SX Kompressor - LC Sprint Vernebler
Tobramycin	Bramitob®	300 mg	4 ml	2 mal 300 mg	eflow® rapid PARI BOY® SX Kompressor - LC Sprint Vernebler[d]
	TOBI	300 mg	5 ml	2 mal 300 mg	eflow® rapid PARI BOY® SX Kompressor - LC Sprint Vernebler; Akita® Jet
	TOBI Podhaler	28 mg		2 mal 4 Kapseln	Trockenpulverinhalator
	Gernebcin®	80 oder 160 mg	2 ml	2 mal 80 - 160 mg	eflow® rapid PARI BOY® SX Kompressor - LC Sprint Vernebler

Wirkstoffe, Dosierungen und Applikationsarten für inhalative Antibiotika bei Mukoviszidose-Patienten mit chronischer Pseudomonas aeruginosa-Infektion und Lungenbeteiligung (modifiziert nach Doring G, Hoiby N, Konstan MW. Consensus statements on inhaled antibiotics for the treatment of cystic fibrosis patients with chronic lung infection by Pseudomonas aeruginosa. Pediatr Pulmonol 2003; 36:

Antibiotikum	Applikation	Mögliche Nebenwirkungen inhalativer Antibiotika
Colistin 2 x 2 MU	Feuchtinhalation	Übelkeit, Erbrechen, Husten, Dyspnoe, Dysphonie, Bronchospasmus, Hämoptysis, Nierenschädigung, Schwindel, Fieber, Resistenzentwicklung
Colistin 2 x 1.66 MU	Trockeninhalation	
Tobramycin 2 x 300 mg	Feuchtinhalation	
Tobramycin 2 x 112 mg	Trockeninhalation	
Aztreonam 3 x 75 mg	Feuchtinhalation	
Gentamycin 2 x 80 mg	Feuchtinhalation	
Ceftazidim 2 x 1 g	Feuchtinhalation	

ÖGP-Empfehlung 2013 – Flick, Pneumologie 2014

LUNGE BAUCH
Amikacin Inhalativ

This study aims to compare the bacterial killing of once- versus twice-daily nebulized amikacin against *Pseudomonas aeruginosa* and to determine the optimal duration of therapy. Three clinical *P. aeruginosa* isolates (amikacin MICs 2, 8, and 64 mg/L) were exposed to simulated epithelial lining fluid exposures of nebulized amikacin with dosing regimens of 400 mg and 800 mg once- or twice-daily up to 7-days using the *in vitro* hollow-fiber infection model. Quantitative cultures were performed. Simulated amikacin dosing regimens of 400 mg twice-daily and 800 mg once-daily achieved ≥2-log reduction in the bacterial burden within the first 24-hours of therapy for all isolates tested. No dosing regimen suppressed the emergence of amikacin resistance. No difference in bacterial killing or regrowth was observed between 3- and 7-days of amikacin. Amikacin doses of 800 mg once-daily for up to 3-days may be considered for future clinical trials.

- **Amikacin 800 mg**
- **1x tgl p inh**
- **über 3 Tage**
- **keine Resistenzvermeidung**

Heffernan, Diag Microbiol Infect Dis 2021

LUNGE BAUCH
Suvratoxumab

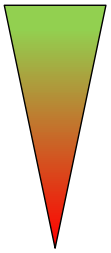
- **25% STAU-VAP's**
- **Suvratoxumab (MEDI4893)**
  - **humaner monoklonaler Antikörper**
  - **Zielstruktur: anti-AT IgG1 gegen Alpha-Toxin**
- **Studie**
  - **multizentr, doppelblinde, placebo-kontroll Phase II**
  - **Suvratoxumab 2.0 g resp 5.0 g einmalig i.v. vs Placebo**

	Placebo group (n=100)	Suvratoxumab 5000 mg group (n=96)	Percentage relative risk reduction (95% CI)	Absolute risk reduction	p value
Incidence of *S aureus* pneumonia	26 (26%)	17 (18%)	31·9 (−7·5 to 56·8)	8·3	0·17
Incidence of all-cause pneumonia	30 (30%)	20 (21%)	30·6 (−4·9 to 54·0)	9·2	0·15
Incidence of all-cause pneumonia or death	42 (42%)	31 (32%)	23·1 (−4·9 to 43·6)	9·7	0·16

KEIN SIGNIFIKANTER BENEFIT

François, Lancet Infect Dis 2021

LUNGE BAUCH
Indikationsspektrum



ERADIKATION	PSAE	Cystische Fibrose
	PSAE	Cystische Fibrose
	PSAE	Bronchiektasien
PROPHYLAXE		Beatmungspneumonie
THERAPIE	4MRGN	Beatmungspneumonie
ERADIKATION	PSAE	Bronchiektasie

LUNGE BAUCH
Fosfomycin

Nebulized Amikacin and Fosfomycin for Severe Pseudomonas aeruginosa Pneumonia: An Experimental Study.

Inhalation REDUZIERT Keimlast im Trachealsekret, jedoch KEIN Einfluss auf das Lungengewebe
KOMBINATION Meropenem und Amikacin/Fosfomycin zeigte KEINE erhöhte PSAE-Aktivität
Reduktion der Resistenzentwicklung möglich

OBJECTIVES: Latest trials failed to confirm benefits of nebulized amikacin for critically ill patients with nosocomial pneumonia. We studied various nebulized antibiotic regimens in a porcine model of severe Pseudomonas aeruginosa pneumonia, related to amikacin, fosfomycin, and susceptible meropenem.

DESIGN: Prospective randomized animal study.

SETTING: Animal Research, University of Barcelona, Spain.

SUBJECTS: Thirty female pigs.

INTERVENTIONS: The animals were randomized to receive nebulized saline solution (CONTROL), nebulized amikacin every 6 hours, nebulized fosfomycin every 6 hours, IV meropenem every 8 hours, nebulized amikacin and fosfomycin every 6 hours, amikacin and fosfomycin every 6 hours, with IV meropenem every 8 hours. Nebulization was performed through a vibrating mesh nebulizer. The primary outcome was lung tissue bacterial concentration. Secondary outcomes were tracheal secretions P. aeruginosa concentration, clinical variables, lung histology, and development of meropenem resistance.

MEASUREMENTS AND MAIN RESULTS: We included female animals into each group. Lung P. aeruginosa burden varied among groups (p < 0.001). In particular, IV meropenem and amikacin and fosfomycin + IV meropenem groups presented lower P. aeruginosa concentrations versus amikacin and fosfomycin, amikacin, CONTROL, and fosfomycin groups (p < 0.05), without significant difference between these two groups undergoing IV meropenem treatment. The sole use of nebulized antibiotics resulted in dense P. aeruginosa accumulation at the edges of the interbronchial septa. Amikacin, amikacin and fosfomycin, and amikacin and fosfomycin + IV meropenem effectively reduced P. aeruginosa in tracheal secretions (p < 0.001). Pathognomonic clinical variables of respiratory infection did not differ among groups. Resistance to meropenem increased in IV meropenem group versus amikacin and fosfomycin + meropenem (p = 0.004).

CONCLUSIONS: Our findings corroborate that amikacin and fosfomycin alone efficiently reduced P. aeruginosa in tracheal secretions, with negligible effects in pulmonary tissue. Combined on of amikacin and fosfomycin with IV meropenem does not increase antipseudomonal pulmonary tissue activity, but it does reduce development of meropenem-resistant P. aeruginosa, in comparison with the sole use of IV meropenem. Our findings imply potential merits for preemptive use of nebulized antibiotics in order to reduce resistance to IV meropenem.

Bassi, Crit Care Med 2019

LUNGE BAUCH
Abklärung & Aufarbeitung

Basisdiagnostik beim ICU-Patienten unterscheidet sich anfangs nicht von dem Normalstationpatienten bzw. Patienten der Notfallaufnahme

- Mikrobiologie & Parasitologie
- Histologie
- Bildgebung
  - Angiographie
  - CT
  - MRT & MRCP
- Endoskopie
  - ERCP
- Chirurgie
  - Lavage
  - Laparoskopie
  - explorative Laparotomie

- Anamnese
- Klinische Untersuchung
- Routinelabor
  - Biomarker (PCT)?
- Bildgebung
  - Abdomen leer
  - Cor/Pulmo
  - Sonographie

- Beiziehung von Fachkonsilien
  - Chirurgie
  - Gynäkologie
  - Infektiologie & Tropenmedizin
  - Innere Medizin
  - Radiologie
  - Urologie
  - …

Watkins, Expert Rev Anti Infect Ther 2012 – Yu, Br J Surg 2013

LUNGE BAUCH
Physiologische Keimflora

Duodenum
KZ 0 – 10^3 KBE/mL
Magenflora, Laktobazillen

Jejunum
KZ 0 – 10^5 KBE/mL
Enterobakterien
Enterokokken, Staphylokokken
Bacteroides, Fusobakterien
Clostridien

Ileum
KZ 10^5 – 10^9 KBE/mL
Enterobakterien
Enterokokken, Staphylokokken
Bacteroides, Fusobakterien
Clostridien

Ösophagus & Magen
KZ <10^3 KBE/mL
transiente Mundhöhlenflora
Fusobakterien, Bacteroides,
Lactobazillen, H. pylori

Dickdarm
KZ 10^{10} – 10^{12} KBE/g
Enterobakterien
Enterokokken, Staphylokokken
Bacteroides, Fusobakterien,
Prevotella, Clostridien
Candida

LUNGE BAUCH
Differentialdiagnosen

- Appendizitis
- Cholezystitis
- PD-Infektion
- obstruktive Cholangitis

- primär
- sekundär
- tertiär

- chronisch
- akut ödematös
- akut nekrotisierend
- infizierte Nekrose

- mesenteriale Ischämie
- Ileus
- Perforation
- Blutung
- Uro-Bauch

LUNGE BAUCH
Rolle der Bakterien

- **Escherichia coli**
  - Letalität
- **Anaerobier**
  - Abszess
- **Enterokokken**
  - Selektion nach ABT
  - "Trittbrettfahrer"
- **Enterobakterien**
  - Selektion nach ABT
  - Resistenz
- **Candida**

Results of implanting single bacterial strains (groups 1–4)

Strain	No. of rats	Mortality (no. died/no. tested)	Abscess (no. with abscess/no. tested)
E. coli	20	13/20 (65%)	0/7
Enterococcus	20	0/20	0/20
B. fragilis	20	0/20	0/20
F. varium	20	0/20	0/20

Results of implanting two bacterial strains (groups 5–10)

Inoculum	Mortality (no. died/no. tested)*	Abscess (no. with abscess/no. studied)*
E. coli + enterococcus	5/20 (25)	0/15
E. coli + *B. fragilis*	7/19 (37)	13/13 (100)
E. coli + *F. varium*	6/19 (32)	12/13 (92)
Enterococcus + *B. fragilis*	0/20	19/20 (95)
Enterococcus + *F. varium*	0/19	17/19 (89)
B. fragilis + *F. varium*	0/19	1/19 (5)

* Numbers in parentheses are percentages.

Onderdonk, Infect Immun 1976

LUNGE BAUCH
Klinik & Keimspektrum

Anzahl an ANTIBIOTIKA und OPERATIONEN steigend

PERFORATION → SEK PERITONITIS → ABSZESS → TERT PERITONITIS

"einfache Entrobakterien" wie *Escherichia coli, Klebsiella pneumoniae*

Anaerbiier wie *Bacteroides fragilis*

Enterokokken

Pseudomonas, "schwierige" Enterobakterien

LUNGE BAUCH
Enterokokken

- Antibiotika mit Enterokokkenlücke als vorherige ABT
- lange Krankenhausaufenthalte mit wechselnder ABT
- schwere Grunderkrankung, Immunsuppression
- Bauch-, herz- oder thoraxchirurgische Eingriffe
- Aufenthalt in Risikoabteilungen (Hämato-Onko, ICU, Transplantchirurgie)
- längere Unterbringung in Altenpflegeheimen
- Mängel in der Basishygiene
- Kontakt zu "Enterokokkenpatienten" oder Oberflächen

Pochhammer, Chirurg 2017

LUNGE BAUCH
Enterokokken & Candida

ENTEROKOKKEN

- Bedeutung kontroversiell beurteilt – Begleitkeim?
- Zunahme resistenter Stämme bis zum VRE
- Co-Pathogen bei E. coli
- Hinweis für Therapieversagen bei polymikrobieller Flora

CANDIDA

- Kolonisation
- Bedeutung beim Drainabstrich
- ABT => höhere oro-enterische Kolonisation
- PPI => höhere Magenbesiedelung
- Wann Pilztherapie

LUNGE BAUCH
Enterokokken

Outcome	*Enterococcal infection group n=119*	*Non-enterococcal infection group n=312*	*Total n=431*	*p*
Initial antibiotic treatment failure, n, %	59 (49.6)	75 (24.2)	134 (31.2)	<0.001
Reoperation, n, %	16 (13.5)	35 (11.2)	51 (11.8)	0.522
Length of ICU stay, [median (IQR)]	6 [3, 11]	4 [3, 8]	4 [3, 8]	0.013
ICU free days [median (IQR)]	10 [0, 27]	8 [5, 15]	9 [4, 16]	0.262
Length of hospital stay, [median (IQR)]	33 [19, 48]	18 [12, 29]	20 [13, 35]	<0.001
Hospital-free days within 28 days [median (IQR)]	9 [0, 18]	14 [5, 18]	14 [3.5, 18]	0.015
ICU mortality, n, %	28 (23.5)	30 (9.6)	58 (13.5)	<0.001
In-hospital mortality, n, %	35 (29.4)	42 (13.5)	77 (17.9)	<0.001
28-day mortality, n%	33 (27.7)	42 (13.5)	75 (17.4)	<0.001

Outcome	*Empirical anti-enterococcal subgroup n=82*	*Non-empirical anti-enterococcal subgroup n=37*	*Total n=119*	*p*
ICU mortality, n%	18 (22.0)	10 (27.0)	28 (23.5)	0.546
In-hospital mortality, n%	22 (26.8)	13 (35.1)	35 (29.4)	0.357
28-day mortality, n%	21 (25.6)	12 (32.4)	33 (33.0)	0.442

Luo, Surg Infect 2021

LUNGE BAUCH
Candida im Bauch

Patienten Typ	z. B. abdominal chirurgische/ internistische Patienten		
Risiko Stratifizierung	Hoch – Mittel – Gering		
Klinische Scores	Hohes Risiko	Geringes Risiko	
Klinische Situation	Sepsis	Infektion	
Therapie	Start	Evaluation	
Mikrobiologische Diagnostik	positiv	negativ	
Biomarker	positiv	negativ	positiv
Therapie Fortführung	weiterführen	stoppen	bedenken

1. Direct microscopy examination for yeast detection from purulent and necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration is recommended in all patients with nonappendicular abdominal infections including secondary and tertiary peritonitis (AII).
2. Samples obtained from drainage tubes are not valuable except for determination of colonization (DIII).
3. Intra-abdominal specimens should be specifically cultured for *Candida* spp. (AII), and species identification should always be requested when *Candida* is isolated (AII).
4. Superficial swabs of abdominal specimens should not be collected for culture (DIII).

Clinical evidence for the use of antifungal therapy for patients with suspected intra-abdominal invasive candidiasis is limited. Most studies are small, uncontrolled, single-center, or performed in specific populations. Patients who have *Candida* species isolated from normally sterile abdominal cultures or drains placed within 24 hours and who have clinical evidence of infection should be treated for intra-abdominal candidiasis. Patients who have had gastroduodenal perforations, anastomotic leaks, necrotizing pancreatitis, or other intra-abdominal events without the isolation of *Candida* species and who are doing poorly despite treatment for bacterial infections may benefit from empiric antifungal therapy. Several meta analyses of

Bassetti, Intensive Care Med 2013 – Pappas, Clin Infect Dis 2016
Kochanek, Dtsch Med Wochenschr 2021

LUNGE BAUCH
ABT adäquat & Source Control rasch

- **ANTIBIOTIKATHERAPIE**
  - 45% Letalität bei inadäquater ABT
  - 16% Letalität bei adäquater ABT
- **SOURCE CONTROL**
  - 90% der Peritonitiden source control erforderlich
  - asap – max 24 Std später ohne Peritonitis & kreislaufstabil
  - Perforation verschließen
  - Peritoneallavage – Keimreduktion
  - Abszesse drainieren

Montravers, Clin Infect Dis 1996 – Koperna, World j Surg 2000

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Chirurgische Vorgehensoptionen

Fokussanierung erfolgreich?

ja → 90 %* → **Relaparotomie „on demand"**

nein → 10 % → **3 chirurgische Therapieoptionen**

- Offenes Abdomen (z. B. abdomineller VAC)
- Dorsoventrale Lavage (kontinuierlich vs. intermittierend)
- Geplante Relaparotomie/ „second look"

Indikationen (Beispiele)

- Abdominelles Kompartmentsyndrom
- Multiple Infektfokusse (Kompartmentierung, nekrotisierende Pankreatitis)
- Intestinale Ischämie, Reevaluation der Perfusion

Schmoch, Chirurg 2019

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Peritonitis

Peritonitisform	Definition	Chirurgische Therapie erforderlich	Erregerspektrum
Primär	Infektion von Aszites durch Translokation ohne Organperforation	Primär nein	Monoinfektion (meist *E. coli*)
Sekundär – ambulant erworben	Organperforation im ambulanten Bereich ohne Voroperation	Ja	Mischinfektion meist ohne resistente Erreger (grampositiv, gramnegativ, Anaerobier)
Sekundär – postoperativ postinterventionell posttraumatisch	Organperforation nach operativem Eingriff/ Intervention/Trauma	Ja	Mischinfektion mit resistenten Erregern (u. a. VRE, ESBL-Bildner, seltener *Pseudomonas* spp.)
Tertiär	Rekurrierende Infektion nach chirurgischer Herdsanierung ohne aktuelle Organperforation	Primär nein	Mischinfektion mit resistenten Erregern (u. a. MRSA, VRE, ESBL-Bildner (3MRGN), *Pseudomonas* spp., *Candida* spp)

Eckmann, Chirurg 2016

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Peritonitis

Peritonitisform/ resistenter Erreger	MRSA	VRE	ESBL- (3MRGN) bildende Enterobacteriaceae	Carbapenem-resistente (4MRGN) Enterobacteriaceae	(MDR) Pseudomonas (3MRGN, 4MRGN)	Acinetobacter spp. (3MRGN, 4MRGN)
Primäre Peritonitis	+	+	+++	–	–	–
Ambulant erworbene sekundäre Peritonitis	–	–	+	–	–	–
Postoperative, postinterventionelle oder posttraumatische Peritonitis	+	++	+++	+	++	+
Tertiäre Peritonitis	+	+++	+++	+	+++	+

Eckmann, Chirurg 2016

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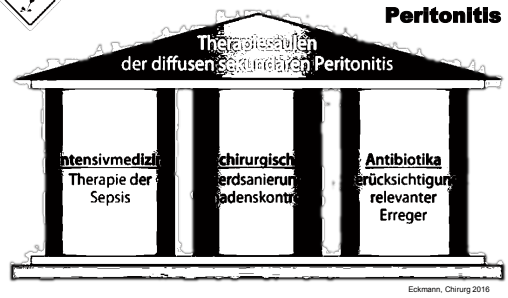
Peritonitis



Eckmann, Chirurg 2016

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Peritonitis

Stufe	Kriterien	Beispiel	Antibiotikatherapie
1 („single shot")	Keine Perforation Keine Peritonitis Ambulant erworben Kein MRE-Risiko Hämodynamisch stabil	Phlegmonöse Appendizitis	Cefazolin, Cefotaxim, Cefuroxim, Ceftriaxon, Ciprofloxacin, Levofloxacin, jeweils + Metronidazol Amoxicillin/Clavulanat Ampicillin/Sulbaktam
2 (3 Tage)	Frische Perforation Lokale Peritonitis Ambulant erworben Kein MRE-Risiko Hämodynamisch stabil	Perforierte Cholezystitis mit Oberbauchperitonitis	Cefazolin, Cefotaxim, Cefuroxim, Ceftriaxon, Ciprofloxacin, Levofloxacin, jeweils + Metronidazol Amoxicillin/Clavulanat Ampicillin/Sulbaktam
3 (5 Tage)	(Diffuse) Peritonitis Ambulant oder nosokomial Individuell unterschiedliches MRE-Risiko Hämodynamisch stabil	Frei perforierte Sigmadivertikulitis mit diffuser frischer Peritonitis	Piperacillin/Tazobaktam Ertapenem Moxifloxacin Tigecyclin
4 (7–10 Tage)	Diffuse Peritonitis Nosokomiale Genese Hämodynamisch instabil Hohes MRE-Risiko	Nahtleckage nach Kolonresektion mit diffuser älterer Peritonitis	Tigecyclin Meropenem, ggf. + Linezolid Imipenem/Cilastatin, ggf. + Linezolid Ceftolozan/Tazobaktam + Metronidazol + antifungale Therapie

Eckmann, Chirurg 2016

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www.antibiotika-app.eu
www.infektiologie.wien