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Febrile neutropenia in paediatric cancer patients

Expert: **Prof Arne Simon**, Universitätsklinikum des Saarlandes, Homburg, Germany

Discussant: **Prof Thomas Lehrnbecher**, University Children's Hospital, Frankfurt am Main, Germany

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Less is more?

Antibiotic stewardship in paediatric oncology

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The German Commission for Hospital Hygiene and Infection Control (KRINKO) recommends (2020):

- Internal Guidelines for Antimicrobial Stewardship in clinical settings specialized in the treatment of immunodeficient / immunocompromised patients should be adjusted to particular issues relevant in this heterogeneous patient population
- The main challenge for the attending oncologists/haematologists, infectious disease specialists and ABS teams is to **identify critical targets for AMS and antifungal stewardship** and to translate the resulting interventions sustainably into clinical practice.
- In Germany the **AWMF Guideline 048/14** concerning the **Diagnostics and Treatment of febrile Neutropenia without a Focus** is currently under revaluation by an expert group from Germany, Austria and Switzerland.

Fever at Diagnosis of Pediatric Acute Lymphoblastic Leukemia: Are Antibiotics Really Necessary?

(*J Pediatr Hematol Oncol* 2015;37:498–501)

Monica Khurana, MD,* Brian Lee, MD,† and James H. Feusner, MD*

Retrospective Analysis of **221 consecutive patients** (2003-2013) **with newly diagnosed ALL** (Children's Hospital & Research Centre Oakland)

- 57% of the patients had fever on / before admission to the hospital
- **Positive blood cultures** were found in = 2 (**1,6%**)

TABLE 1. Summary of Patients ± Fever and ± Neutropenia

	ANC ≤ 500	ANC > 500	Total
Febrile	55 (67%)	71 (51%)	126
Afebrile	27	68	95
Total	82	139	221

Most patients presented with fever but not neutropenia. Among neutropenic patients, the majority of them were febrile.

ANC indicates absolute neutrophil count.

Fever at Diagnosis of Pediatric Acute Lymphoblastic Leukemia: Are Antibiotics Really Necessary?

(*J Pediatr Hematol Oncol* 2015;37:498–501)

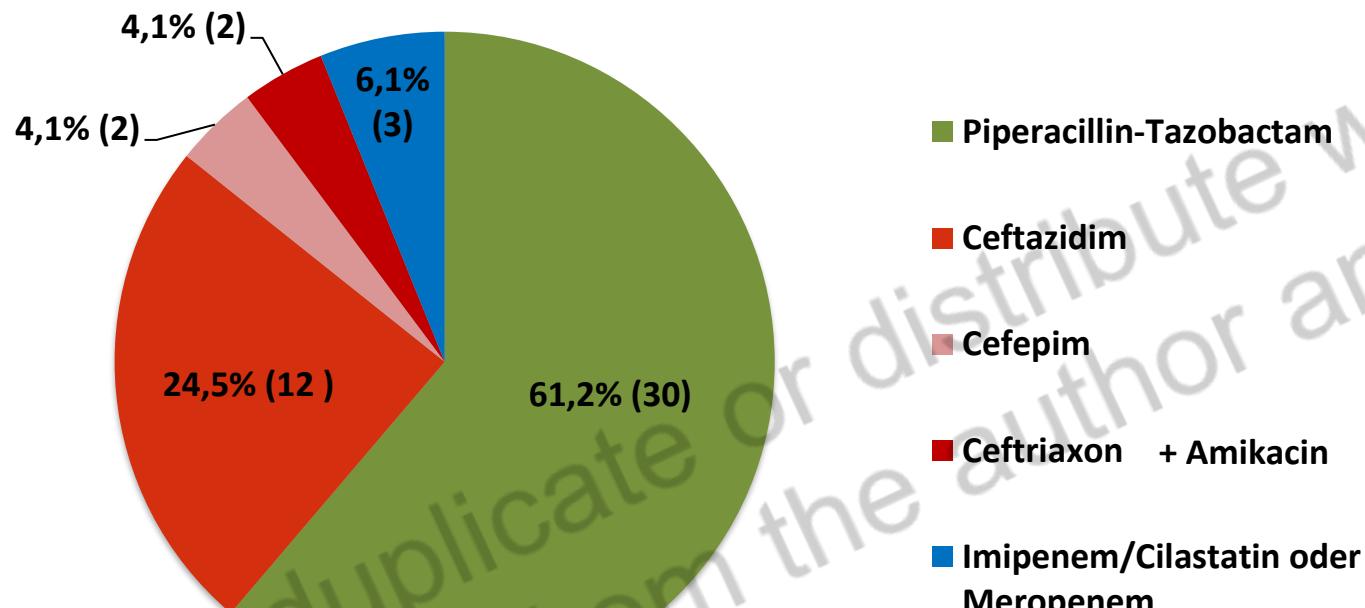
Monica Khurana, MD,* Brian Lee, MD,† and James H. Feusner, MD*

Target ABS conclusion:

In paediatric patients with newly diagnosed ALL and fever:

- In-depth search for a serious bacterial infection incl. blood culture, were clinically applicable: urine and stool culture, and viral PCRs from respiratory samples, chest X-ray
- In case of negative blood cultures and clinical response to ABT
→ consider ABT cessation after 3 days (irrespective of neutrophil counts)

First line ABT in febrile neutropenia



Scheler M, Lehrnbecher T, Groll A, Volland R, Laws H, Ammann R, Agyeman P, Attarbaschi A, Lux M, Simon A (2020) Management of children with fever and neutropenia: results of a survey in 51 pediatric cancer centers in Germany, Austria, and Switzerland. *Infection* 48:607-618

First-line treatment of FUO

Target ABS conclusion:

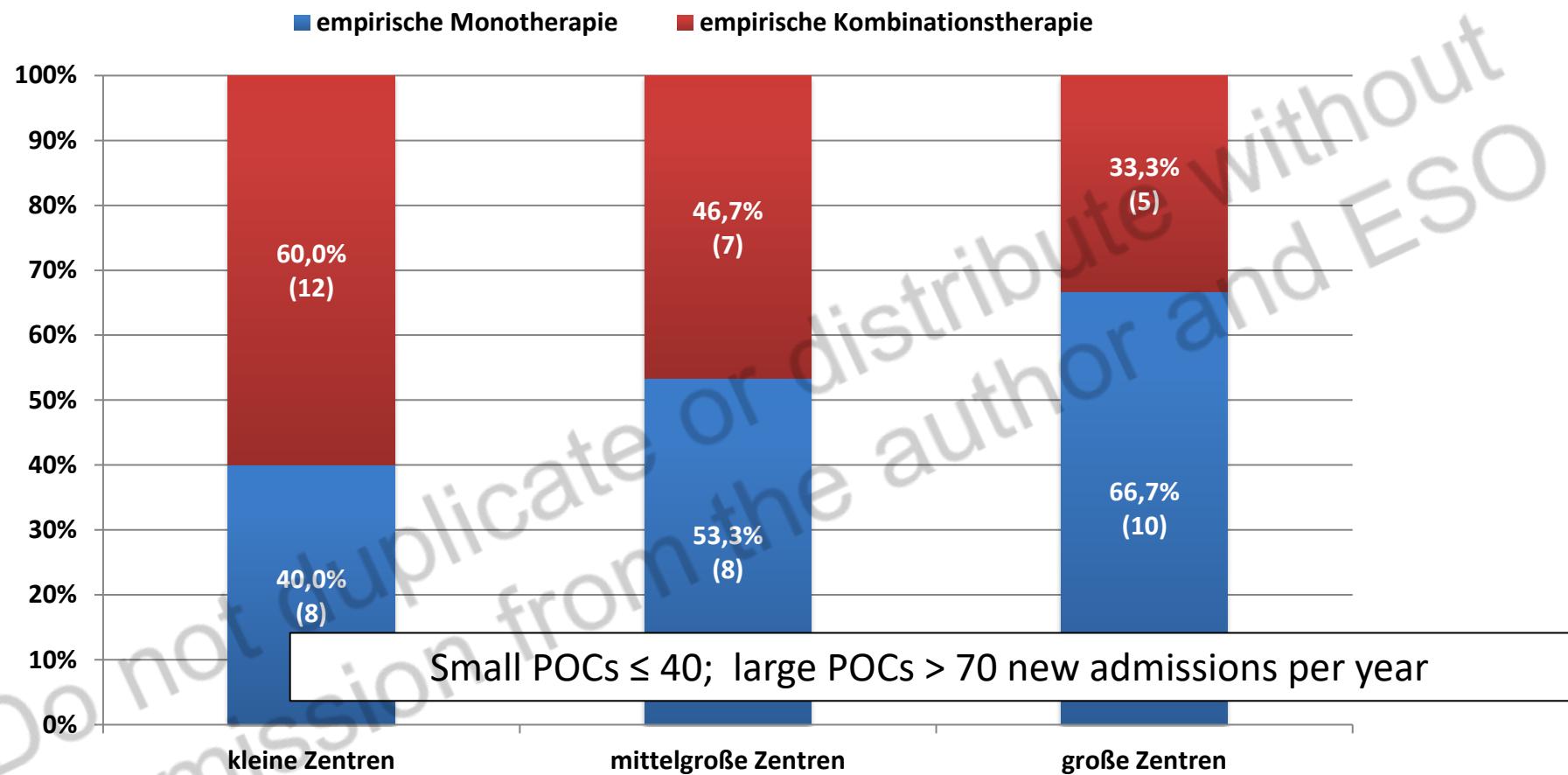
Using Ceftazidime or Cefepime as first-line treatment may increase the selective pressure on multidrug-resistant gramnegative pathogens (MRGN) and viridans group streptococci (STRV).

Cefepim is an adequate alternative in patients with Pip-Taz-related adverse drug reactions (exanthema, prolonged neutropenia)

Meropenem as first line treatment should only be considered

- In patients, who are colonised with MRGN
- In all patients with clinical signs of sepsis (not in FUO)

Empirical monotherapy in only 52% of 51 POCs



Scheler M, Lehrnbecher T, Groll A, Volland R, Laws H, Ammann R, Agyeman P, Attarbaschi A, Lux M, Simon A (2020) Management of children with fever and neutropenia: results of a survey in 51 pediatric cancer centers in Germany, Austria, and Switzerland. *Infection* 48:607-618

In which FUO patients may first line combination ABT be considered ?

- ALL, prolonged neutropenia (> 10 days), high dose steroids (ALL induction, HR-cycles, patients with relapsed leukaemia);
- transient low mean arterial RR responding to a volume bolus without the need for catecholamines;
- increased risk of bacterial translocation, e.g. severe mucositis, perianal skin or soft tissue lesions.
- POCs with higher rates of GNP resistance against Pip-Taz (> 20%?)
- A first line **combination therapy with a glycopeptide** should be considered
 - in patients with leukaemia (AML, ALL) after high dose cytarabine
 - in patients with skin- and soft tissue infection (e.g. allocated to the long term central venous access catheter; CVAD; Broviac/Hickman/Port)
 - patients with previously known MRSA colonisation

Aminoglycoside use in paediatric febrile neutropenia – Outcomes from a nationwide prospective cohort study

Brendan J. McMullan^{1,2,3*}, Gabrielle M. Haeusler^{1,4,5,6,7,8}, Lisa Hall⁹, Louise Cooley¹⁰, Andrew J. Stewardson¹¹, Christopher C. Blyth^{12,13,14,15}, Cheryl A. Jones^{16,17,18,19}, Pamela Konecny^{20,21}, Franz E. Babi^{18,22,23,24}, Françoise Mechinaud^{25,26}, Karin Thrusky^{1,27,28}, on behalf of the Australian PICNICC study group and the PREDICT network¹¹

Australian Predicting Infectious ComplicatioNs in Children with Cancer (PICNICC)

In this network, severe infections due to MRGN are rare events

Prospective study (8 POCs) Children and adolescents with caner(Nov. 2016- Jan. 2018),

858 FN-events in n = 462 children and adolescents

In total, **255 aminoglycoside (AGL) treatment cycles (in 29.7% of all FUO events)**

Low adherence to national guidelines concerning the decision for or against AGL use

Any measurable effect of AGL combination treatment (during the first 12 hours)?

Multivariate adjusted analysis revealed a significantly higher risk for an adverse outcome in patients with combination treatment (aHR 3.81 CI95% 1.89-7.67).

No increased risk of unfavourable outcome in eligible patients who did not receive aminoglycosides.

Gentamicin dosing and therapeutic target

- GPOH/DGPI AWMF guideline (Reg. No. 048/14)
250 mg/m² BSA (max. 10mg/kg, max. 400mg) as once-daily infusion (30 min). Cmax target 15-20 mg/L (sampling 1 h after the second dose),
< 2mg/L after 8-10 hours and through level < 1 mg/L
- Bialowski et al. PIDJ 2016; 38 (6) 693-698
 ≤ 10 years 10,8 mg/kg (= 324 mg/m² KOF) max. 360 mg
 > 10 Jahre 6,4 mg/kg (=192 mg/m² KOF) max. 360 mg
Cmax target 25-40 mg/L, C through < 2mg/L

Target ABS conclusion:

There seems to be no genuine oto- or nephrotoxicity after short term treatment with AGL (≤ 72 h) and single daily dosing.

Consider contraindications for AGLs:

pre-existing inner ear ototoxicity, severe neuropathy,
pre-existing renal impairment, including
chemotherapy induced Fanconi syndrome.

Antimicrobial stewardship in paediatric oncology: Impact on optimising gentamicin use in febrile neutropenia

Stefanie Hennig¹  | Christine E. Staatz¹ | Daniel Natanek¹ | Sabina Bialkowski¹ |
Carolina Consuelo Llanos Paez¹  | Rachael Lawson² | Julia Clark³ 

Retrospective analysis of 453 FUO-events in 227 paed. cancer patients
After a change in the internal guideline to a **preferred monotherapy with Pip-Taz**, the proportion of ABT cycles with AGL combination treatment decreased from **79%** to **21%** ($P < 0,001$).

The proportion of AGL cycles without therapeutic drug monitoring (TDM) decreased from 44% to 0% ($P < 0,001$)

Hennig S. Pediatr Blood Cancer 2018; 65 (2)

Target ABS conclusion :

Empiric first-line combination treatment with AFLs should be regularly discontinued after 72 hours in clinically stable patients with negative blood cultures or a BC results which allows a targeted monotherapy.

Restricted use of glycopeptides in paediatric cancer patients with fever and neutropenia

Arne Simon ^{a,*}, Nora Gröger ^a, Anja Wilkesmann ^a, Carola Hasan ^a,
Gertrud Wiszniewsky ^a, Steffen Engelhart ^b, Michael H. Kramer ^b, Udo Bode ^a,
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^a Department of Pediatric Hematology and Oncology, Children's Hospital Medical Center, University of Bonn,
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^c Division of Pediatric Hematology and Oncology, University Children's Hospital, Bern, Switzerland

Received 29 March 2006; accepted 27 June 2006

Sustained reduction of teicoplanin use

Target ABS conclusion :

Combination treatment with a glycopeptide (Vancomycin, Teicoplanin) should be discontinued after 72 h if the blood cultures have not yielded a methicillin-resistant grampositive pathogen or STRV.

Fosfomycin may be used alternatively to glycopeptides in patients with persistent fever (≥ 72 h; 150-300mg/kg/d in 3 single doses)

Hepping N. & Simon A. Fosfomycin in paediatric cancer patients: a feasible alternative to glycopeptides? Int J Antimicrob Agents 2009; 33: 389

Brief Report

Assessment of Initial Vancomycin Dosing in Pediatric Oncology Patients

Hillary Orr ^{1,2,*}, Deni Trone ^{1,3}, Joshua Elder ¹ and Ashok Raj ⁴

- Retrospective audit (Houston, Tx) concerning the vancomycin pharmacokinetics in 56 paed. cancer patients (60 mg/kg/day)
- **targeted therapeutic concentrations between 10-20 mg/L**
- **Twelve patients (21%) achieved 10-20 mg/L**, while 44 patients (79%) obtained trough levels below 10 mcg/mL despite the addition of nephrotoxic agents.

Target ABS conclusion:

- In children with normal (or augmented) renal clearance, the vancomycin starting dose should be 60mg/kg/d (not 40mg/kg/d)
- the most appropriate trough level (e.g. before the 3. dose) is still controversial.

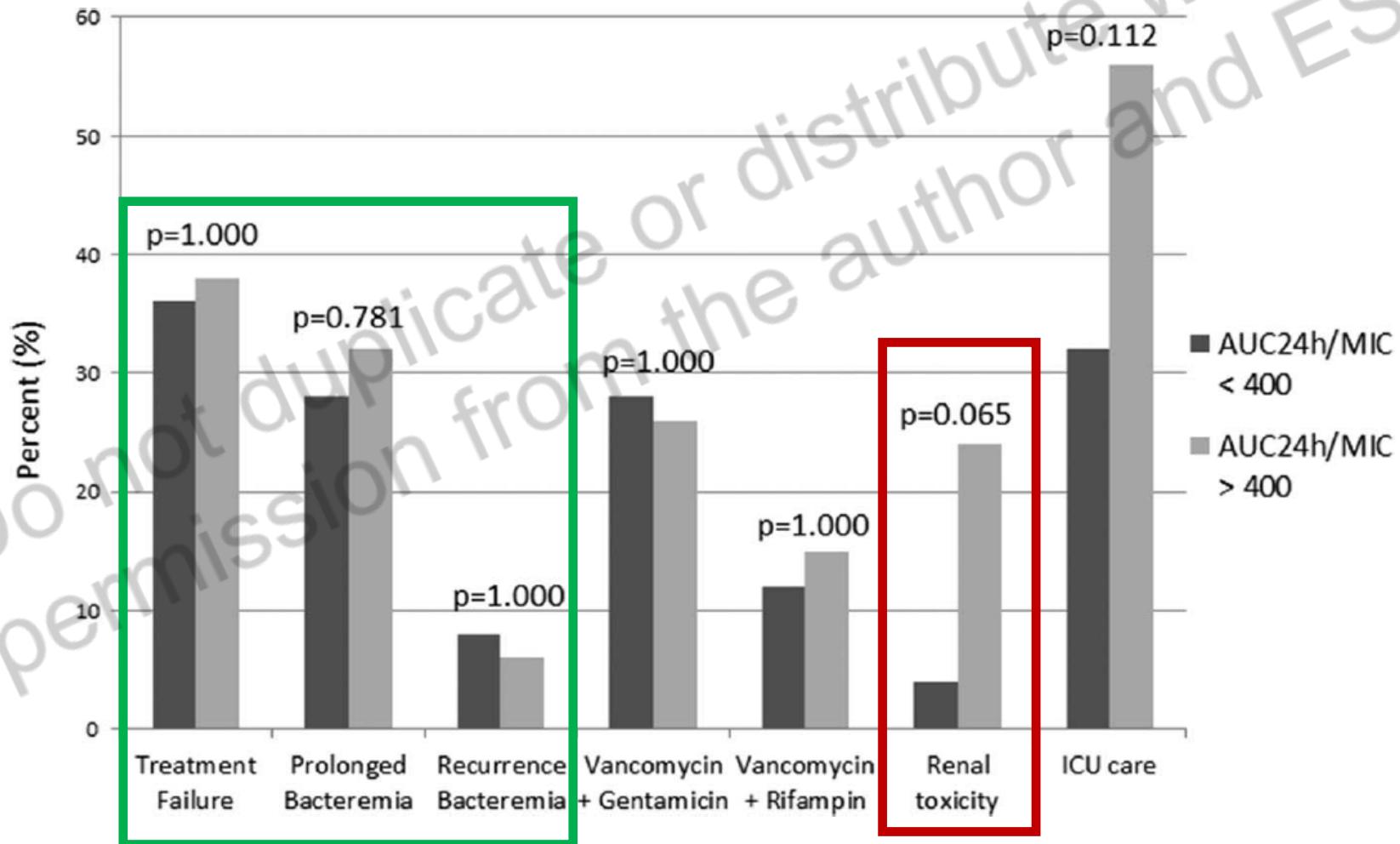
Orr H, et al. Children (Basel, Switzerland) 2017; 4

Refer to Zhao W et al. Antimicrob Agents Chemother 2014; 58: 3191-3199

Evaluation of Target Attainment of Vancomycin Area Under the Curve in Children With Methicillin-Resistant *Staphylococcus Aureus* Bacteremia

Ther Drug Monit 2015;37:619–625

Andrea Hahn, MD,* Robert W. Frenck, Jr, MD,†‡ Mary Allen-Staat, MD, MPH,†‡ Yuanshu Zou, PhD,§ and Alexander A. Vinks, PharmD, PhD‡¶



Population pharmacokinetics and dosing optimization of teicoplanin in children with malignant haematological disease

Wei Zhao,^{1,2,3,4} Daolun Zhang,³ Thomas Storme,⁵
André Baruchel,⁶ Xavier Declèves⁷ & Evelyne Jacqz-Aigrain^{1,3,4}

85 paed cancer patients.

- Dosing 10 mg/kg (3 times every 12 h, than once daily)
- **through levels below 10 mg/L in 48%**

→ maintenance dosing 15 mg/kg/d?

→ Therapeut. target?

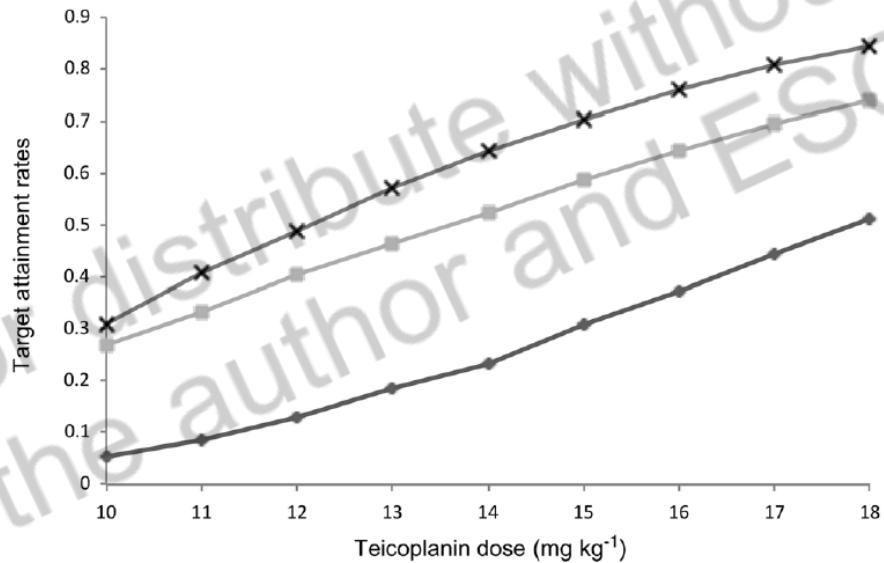


Figure 3

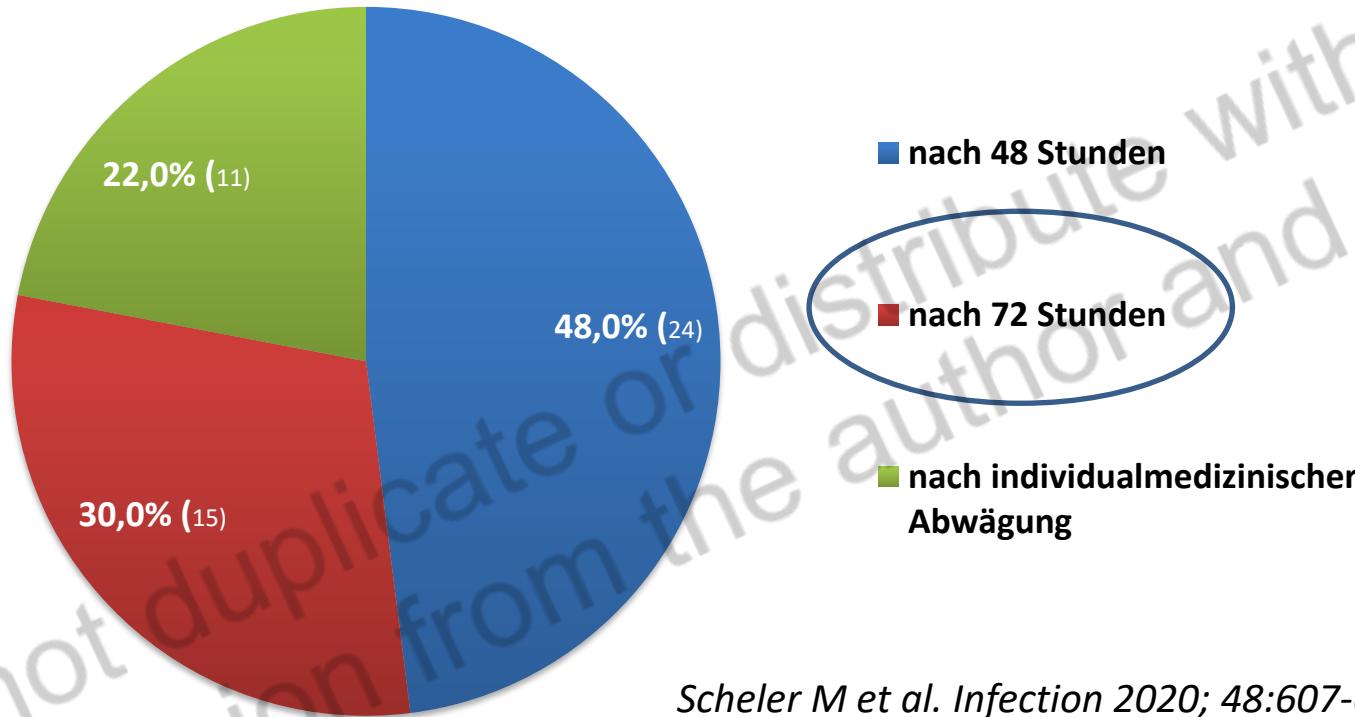
Target attainment rates. Target attainment rates for the 100 simulated trials are presented as a function of dose and age group. The AUC target is 750 mg L⁻¹ h. infants ●, children ■, adolescents ✖

Effect of concomitant vancomycin and piperacillin-tazobactam on frequency of acute kidney injury in pediatric patients

- AKI = increase of serum creatinine of 50% or $\geq 0,5$ mg/dl
- 100 children with Vanco-Pip/Taz (including 37 with febrile neutropenia) v.s. 374 children with Vanco + another Betalactam-antibiotic
- Median Vancomycin dose in both groups: 60 mg/kg/d
- **Incidence AKI 27% vs. 7% ($p < 0.0001$) OR 5.96 (CI95% 2.77 -12.78)**
- The latency from ABT-start to AKI was shorter in the Vanco/Pip-Taz group 3.8 vs. 7.9 days ($P = 0,0065$)
- **Vanco-through levels > 20 mg/L increased the risk of AKI (OR 7.5)** and was more prevalent in the Vanco/Pip-Taz group (17% vs. 2.7%)

Buhlinger KM. et al. Am J Health Syst Pharm 2019; 76: 1204-1210
Downes KJ. Et al. JAMA Pediatr 2017; 171: e173219

When should the first line therapy be escalated in a stable patient?

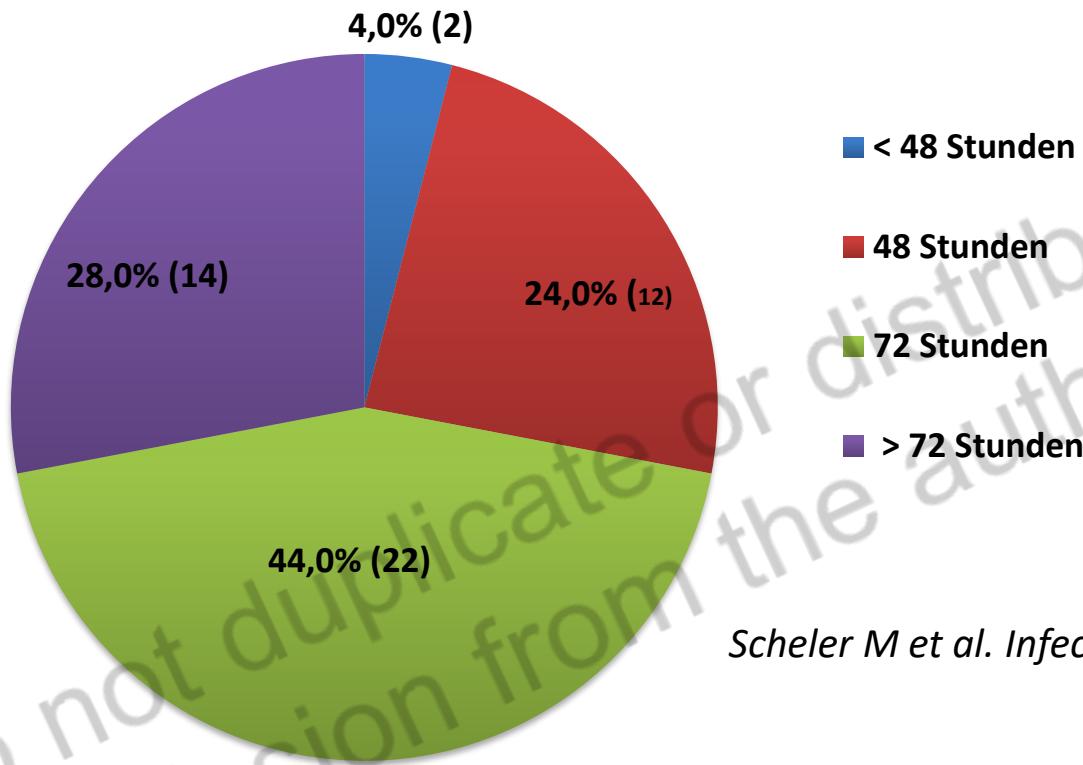


Scheler M et al. Infection 2020; 48:607-618

Target ABS conclusion:

Persistent fever alone without any change in the clinical appearance/condition is no mandatory reason to escalate ABT. This applies in particular to patients, in whom the PBC-count is expected to recover during the next days.

What is the minimal duration of IV treatment?



42% of the POCS wait with the cessation of ABT until neutrophils recover.

Scheler M et al. Infection 2020; 48:607-618

Target ABS conclusion: After a minimal duration of 72 h, IV ABT can be stopped in clinically stable low risk FUO patients without fever for at least 24 hours irrespective of neutrophil counts. The patient can leave the hospital on the same day unless no other reasons necessitate inpatient treatment.

Antibiotic prophylaxis in children undergoing abdominal surgery for neoplastic diseases

Luca Pio^{1,2}, Stefano Avanzini², Irene Paraboschi¹, Michela Wong¹, Aldo Naselli¹, Alberto Garaventa³, Massimo Conte³, Ubaldo Rosati⁴, Giuseppe Losurdo⁵, Giuseppe Fratino¹, Giuseppe Martucciello^{1,2}, Girolamo Mattioli^{1,2}, Elio Castagnola⁵

- Retrospective analysis from Genova (2008-2016) evaluating the incidence of surgical site infections (SSI)
145 paediatrics cancer patients up to 30 days after intraabdominal tumor resection (median age 4 years)
- **Cefazoline** 25 mg/kg (max. 2 g) 30 min before the operation plus 2 additional doses in 24 h
- No SSI observed

Pio L. et al. Infez Med 2018; 26: 122-125

Target ABS conclusion:

Reconsider your institutional practice of perioperative antibiotic prophylaxis: do not use broad spectrum antibiotics, do not administer any PAP for more than 24 hours

Blood Stream Infections and Antibiotic Utilization in Pediatric Leukemia Patients With Febrile Neutropenia

James Reinecke, MD,* Stefanie Lowas, MD,† Jessica Snowden, MD,‡
and Kari Neemann, MD,‡

- 67 PC-patients,
21 ALL and 11 AML
- 197 febrile neutropenia events
- n= 36 (18%) positive blood culture (→ MD-BSI)
- PICU n=5 (2,5%)
- Attributable mortality 1/197 (0,5% of all FN)
1/ 36 (2,8% of all MD-BSI)

- Cefepime
- Meropenem
- Cefepime + aminoglycoside
- Piperacillin-tazobactam
- Cefepime + Vancomycin
- Other (e.g. Metronidazol)



De-escalation

→ possible in 25/36 MD-BSI (63%) concerning in vitro sensitivity and in 19/25 (72%) on clinical grounds, respectively.
→ eventually performed in 9 of 19 (47%) without any negative impact on outcome

Meropenem Use in Pediatric Oncology – Audit on Indication, Appropriateness and Consumption Comparing Patient Derived and Pharmacy Dispensing Data

Meropenem in der Kinderonkologie – Audit zum angemessenen Einsatz sowie zum tatsächlichen Verbrauch im Vergleich mit Apothekenlieferdaten

Authors

Svenja Ockfen¹, Leonie Egle¹, Katharina Sauter², Manfred Haber³, Sören L. Becker⁴, Gudrun Wagenpfeil⁵, Norbert Graf⁶, Arne Simon⁶

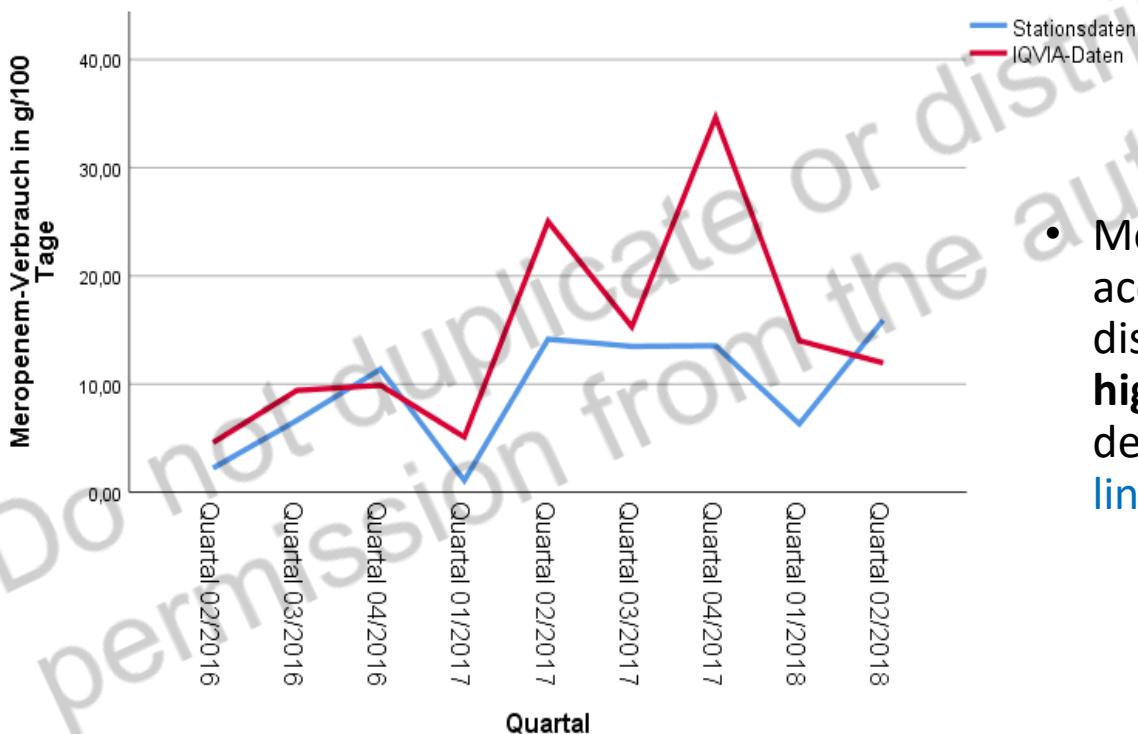
- Of 235 consecutive paediatric cancer patients, 45 (19%) received at least one cycle of meropenem, comprising 57 FN events.
- Preceding the use of meropenem, only **5% of patients were known to be colonized with multidrug-resistant Gram-negative pathogens.**
- In 5 of 57 FN events (8.8%), initial blood cultures yielded a Gram-negative pathogen. Concerning definite treatment, appropriate alternatives to meropenem with a smaller spectrum of activity would have been available in 4 cases, but a de-escalation was not performed.
- The median length of therapy in the meropenem group was 6 days, the corresponding median for days of therapy (DOT) was 12 days (53% combination ABT)

Meropenem Use in Pediatric Oncology – Audit on Indication, Appropriateness and Consumption Comparing Patient Derived and Pharmacy Dispensing Data

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- Meropenem-consumption according to pharmacy dispensing data **1,94-times higher** (red line) than patient-derived real consumption (blue line)

Preventive bundles

... to avoid CVAD-related bloodstream infections are very effective in paediatric oncology

Research Article

Impact of a modified Broviac maintenance care bundle on bloodstream infections in paediatric cancer patients

Einfluss eines modifizierten Präventionsbündels auf Broviac-assozierte Blutstrominfektionen bei kinderonkologischen Patienten

- ✉ **Rhoikos Furtwängler** - Department of Paediatric Oncology and Haematology, University Hospital, Homburg/Saar, Germany
- ✉ **Carolin Laux** - Department of Paediatric Oncology and Haematology, University Hospital, Homburg/Saar, Germany
- ✉ **Norbert Graf** - Department of Paediatric Oncology and Haematology, University Hospital, Homburg/Saar, Germany
- ✉ **Arne Simon** - Department of Paediatric Oncology and Haematology, University Hospital, Homburg/Saar, Germany

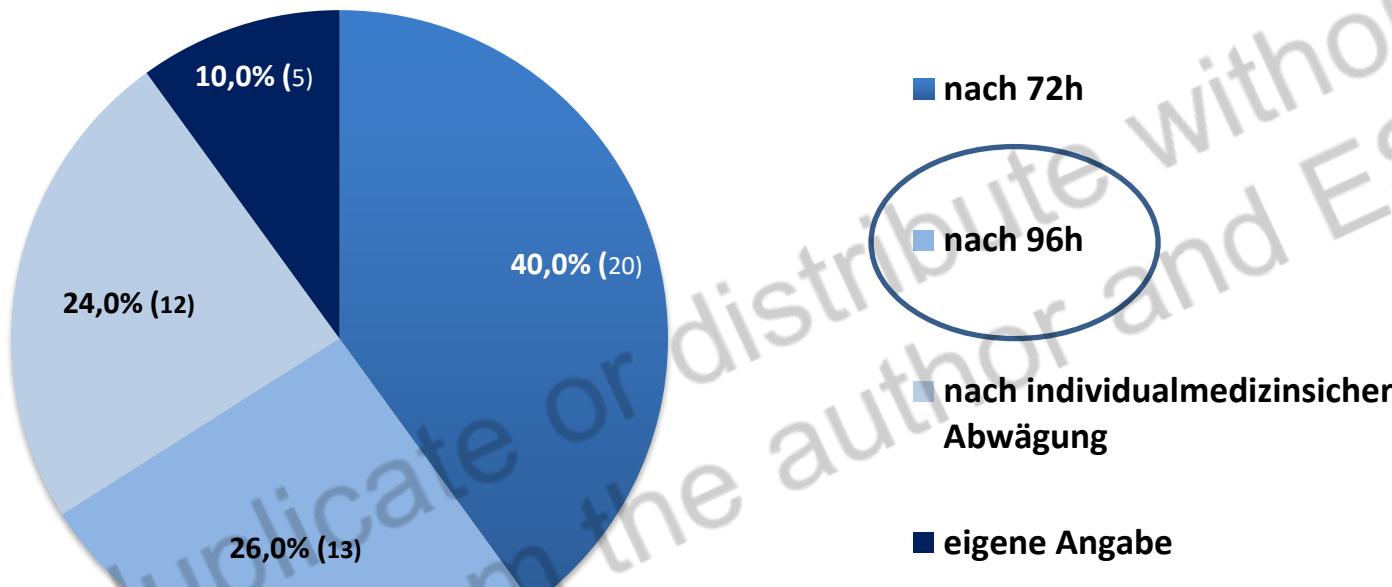
GMS Hyg Infect Control 2015;10:Doc15

doi: 10.3205/dgkh000258  urn:nbn:de:0183-dgkh0002581 



*Furtwängler R, Laux C, Graf N, Simon A. GMS hygiene and infection control 2015; 10: Doc15
<https://www.egms.de/static/en/journals/dgkh/2015-10/dgkh000258.shtml>*

Empirical antifungal treatment



Scheler M et al. Infection 2020; 48:607-618

Retrospective Audit: Systemic antifungal treatment



ISSN: 2637-9627

Annals of Pediatrics

Open Access | Research Article

Systemic Antifungal use in a Pediatric Cancer Center - Audit Comparing Pharmacy Dispensing Data with Patient - Derived Consumption

Katharina Sauter¹; Leonie Egle¹; Svenja Ockfen¹; Manfred Haber²; Sören L Becker³; Gudrun Wagenpfeil⁴; Norbert Graf¹; Arne Simon¹

- **18.7% of 203 consecutive paediatric cancer patients (April 2016 - June 2018) received at least one cycle of systemic antifungal treatment** (in total 86 cycles).
- Prophylaxis in HR-patients during neutropenia: Micafungin or liposomal Amphotericin B 2-times a week (outpatient clinic)
- Empirical treatment (FUO) with Caspofungin liposomal Amphotericin B in HR-patients with fever persisting for ≥ 96 h
- No IFIs related mortality during this period (cave: no allogeneic SCT)

Antimicrobial Stewardship Barriers and Goals in Pediatric Oncology and Bone Marrow Transplantation

Survey including 97 ABS practitioners from at least 45 institutions in the United States, Australia, New Zealand, Mexico, and Canada

344 INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY MARCH 2016, VOL. 37, NO. 3

TABLE 1. Antimicrobial Stewardship Goals in Pediatric Oncology From 97 Respondents

Goal	n ^a	(%)	Respondents more likely to report goal
Reduce time to antimicrobial de-escalation	72	(74)	Australasian (OR, 4.2 [95% CI, 1.1–15.7])
Avoid initiation of unnecessary antibiotics	60	(62)	
Reduce redundant coverage	51	(53)	
Guideline development	36	(37)	
Clinician education	28	(29)	
Reduce time to appropriate therapy for resistant infection	18	(19)	ASP work effort <10% (OR, 3.5 [95% CI, 1.1–10.6])
Prevent adverse effects	13	(13)	
Reduce antimicrobial costs	7	(7)	
Promote switch from IV to oral antibiotics	4	(4)	

NOTE. ASP, antimicrobial stewardship program; ASP work effort, proportion of work effort dedicated to antimicrobial stewardship; IV, intravenous; OR, odds ratio.

^an = number of respondents reporting this as one of their top 3 antimicrobial stewardship goals in pediatric oncology.

Antimicrobial Stewardship Barriers and Goals in Pediatric Oncology and Bone Marrow Transplantation

TABLE 2. Barriers to Antimicrobial Stewardship in Pediatric Oncology From 97 Respondents

Reported barrier	Any		Important		Respondents more likely to report barrier
	n	(%)	n	(%)	
Barriers related to the antimicrobial stewardship program					
1. Insufficient data analysis resources	81	(84)	51	(53)	ASP work effort $\geq 10\%$ (OR, 3.2 [95% CI, 1.2–8.3])
2. Insufficient clinician time assigned to antimicrobial stewardship	77	(79)	50	(52)	
3. ASP does not have enough power or authority	67	(69)	45	(46)	ASP work effort $\geq 10\%$ (OR, 2.9 [95% CI, 1.1–7.6])
Barriers related to oncology clinicians					
1. Oncology clinicians are more motivated by fear of rare adverse outcomes than long-term risks of antimicrobial use	86	(89)	72	(74)	
2. Oncology clinicians are confident in their antibiotic	84	(87)	50	(52)	
Barriers related to infection treatment protocols					
1. Oncology clinicians follow externally derived collaborative group protocols	N/A		46	(47)	
2. Insufficient ID or ASP input into local clinical practice guidelines	N/A		41	(42)	

Excerpt from Tab. 2 of the cited article

Wolf J et al. Pediatric Hematology/Oncology Antimicrobial Stewardship Interest Group. Infect Control Hosp Epidemiol. 2016 Mar;37 (3) 343-7

Final case

- 6-year old boy with neurogenic bladder dysfunction due to a spinal medulloblastoma metastasis, suprapubic urinary catheter
- Urine culture: *Pseudomonas spp.* ($\geq 10^5$ CFU/ml)
- Just finished a chemo cycle, declining neutrophils

Kultur

[1] *Pseudomonas* sp.

(*Pseudomonas corrugata*)

10^5 /ml

Antibiogramm	[1]		[1]
Piperacillin/Tazobactam	I	Ciprofloxacin	I
Ceftazidim	I	Levofloxacin	I
Cefepim	I	Amikacin	S
Imipenem	I	Tobramycin	S
Meropenem	S		

Die Durchführung der Resistenztestung und die Interpretation in S / I / R erfolgt für Bakterien nach EUCAST (www.eucast.org), für Hefepilze nach CLSI.

Wichtige Änderung der bakteriellen Resistenztestung nach EUCAST:

I im Antibiogramm bedeutet nicht mehr intermediär im Sinne einer verminderten Empfindlichkeit. Sowohl **S** als auch **I** bedeuten in Zukunft **sensibel**, jedoch mit einer Dosierungsempfehlung zur Therapieoptimierung: S = sensibel bei normaler Exposition, I = sensibel bei erhöhter (increased) Exposition. Ein mit I gekennzeichnetes Antibiotikum ist bei korrekter Dosierung ebenso wirksam wie ein mit S gekennzeichnetes. Bitte berücksichtigen Sie dies bei der Auswahl von Antibiotika!

Dosierungshinweise: www.uks.eu/abs

Final case

Nachrichtenbl. Deut. Pflanzenschutzd., 34 (6), S. 81–82, 1982, ISSN 0027-7479.
© Eugen Ulmer GmbH & Co., Stuttgart

Biologische Bundesanstalt für Land- und Forstwirtschaft, Institut für Mikrobiologie, Berlin-Dahlem

Erster Nachweis von *Pseudomonas corrugata* als Erreger der „Stengelmarkbräune“ der Tomate in der Bundesrepublik Deutschland

First occurrence of *Pseudomonas corrugata* as a causal agent of tomato pith necrosis in the Federal Republic of Germany

Von S. Köhn

