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WE DEVELOP FOR PATIENTS
Afabicin
Staphylococcus-**specific**,
microbiota sparing
March 2023


Next challenge
Antimicrobial resistance:
the silent pandemic

A global health problem

AMR: One of 21st century's greatest threats to health

SUPERBUGS ARE A MAJOR THREAT :
MRSA, CRE, *N. gonorrheae*, *A. baumanii*…

"…a health problem whose magnitude is at least as large as major diseases such as HIV and malaria, and potentially much larger."

Antimicrobial Resistance Collaborators, 2022

WORLDWIDE[1]

1.27 million deaths in 2019 due to bacterial AMR

UNITED STATES[2]

>2.8 million antibiotic-resistant infections

>35,000 deaths/year

EUROPE[3]

33,000 deaths in 2015

AMR, antimicrobial resistance; CRE, carbapenem-resistant Enterobacterales; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus.*

1. Antimicrobial Resistance Collaborators. *Lancet*. 2022;399(10325):629-655. 2. CDC Antibiotic resistance threats in the United States, 2019.
3. Cassini A, et al. *Lancet Infect Dis*. 2019;19(1):56-66.

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A key AMR driver

Inappropriate antibiotic use is a major driver of AMR[1]

↑ **Selection pressure from antibiotic use**

46% Increase in antibiotic consumption worldwide from 2000 to 2018[2]

30% Of outpatient antibiotic prescriptions in the US are **inappropriate**[3]

The quality of antibiotic prescribing, especially spectrum of activity, is a critical antibiotic stewardship factor associated with AMR[4]

AMR, antimicrobial resistance; MRSA, methicillin-resistant *Staphylococcus aureus.*

1. Holmes AH, et al. *Lancet*. 2016;387(10014):176-187. 2. Browne AJ, et al. *Lancet Planet Health*. 2021;5(12):e893-e904.
3. Fleming-Dutra KE, et al. *JAMA*. 2016;315(17):1864-1873. 4. Borg MA, et al. *Microb Drug Resist.* 2021;27(7):889-894.

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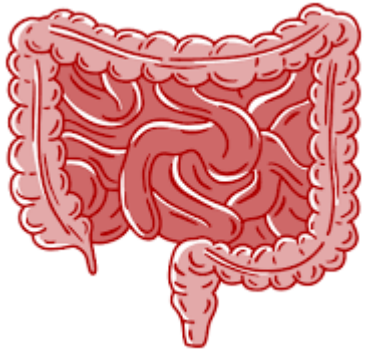
The gut – an AMR reservoir

Antibiotic-induced dysbiosis expands and sustains AMR



Consequences of broad-spectrum antibiotic use for the gut microbiota include:[1-3]

- Reduced bacterial diversity
- Selection for resistant bacteria
- Promotion of genetic information transfer among bacteria
- Intrusion of pathogenic organisms, leading to superinfection (e.g., *Clostridium difficile*-induced colitis)

Use of targeted, microbiota-sparing antibiotics should be promoted to treat common conditions and help control antibiotic resistance[4,5]

AMR, antimicrobial resistance

1. Modi SR, et al. *J Clin Invest.* 2014;124:4212-4218. 2. Bhalodi AA, et al. *J Antimicrob Chemother.* 2019;74:i6-i15.
3. Anthony WE, et al. *J Infect Dis.* 2021;223:S209-13. 4. Alm RA, Lahiri SD. *Antibiotics.* 2020;9(7):418.
5. Diamantis S, et al. *Antibiotics.* 2022;11(7):924

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A call to action

Fighting AMR is a global effort

WHO Global Action Plan Objectives


Improve awareness and understanding of antimicrobial resistance


Strengthen surveillance and research


Reduce the incidence of infection


Optimize the use of antimicrobial medicines


Ensure sustainable investment in countering antimicrobial resistance

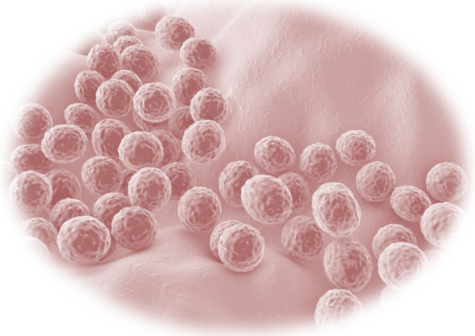
AMR, antimicrobial resistance; WHO, World Health Organization.
WHO. Global Action Plan on Antimicrobial Resistance. 2015.

Staphylococcus infections

Unmet medical need

A ubiquitous pathogen

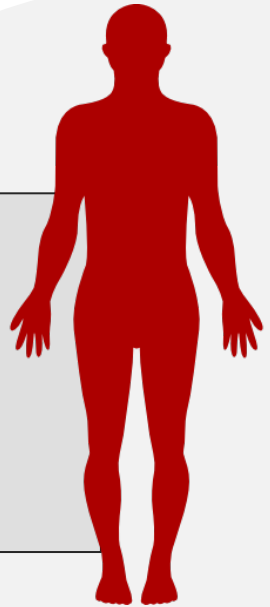
Staphylococci cause a variety of life-threatening infections



- ***S. aureus***
- **CoNS**

Infections include:[1,2]

- Bone and joint infections
- Endocarditis
- IV catheter infections
- Skin and soft-tissue infections

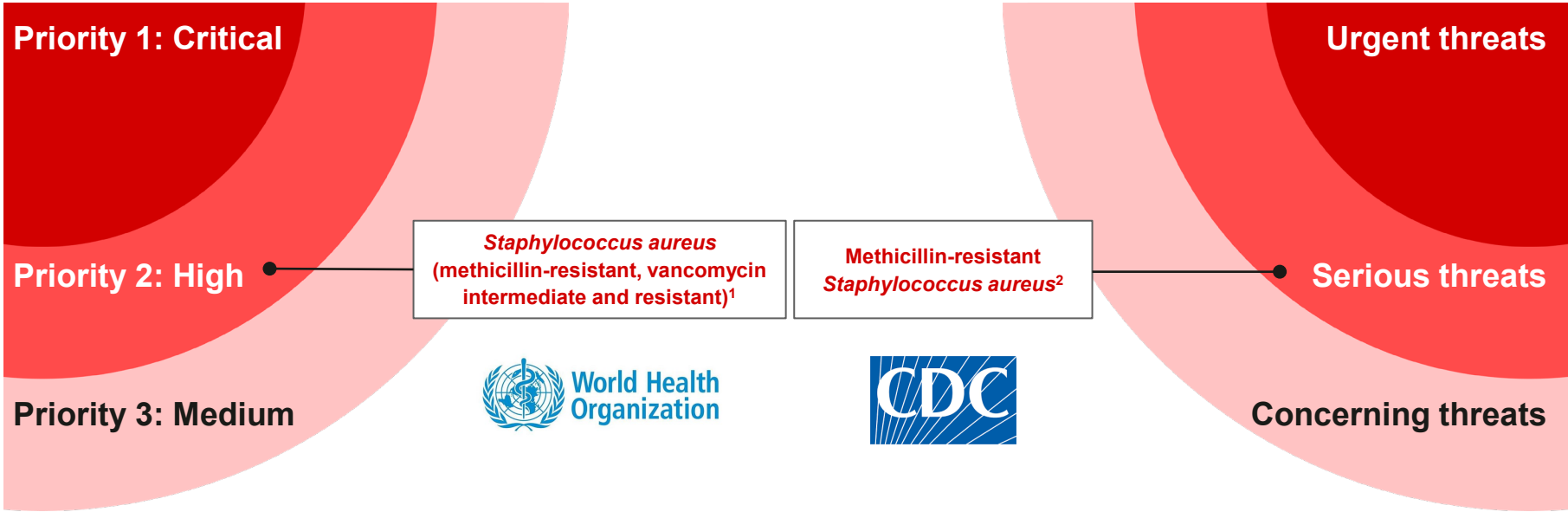


CoNS, coagulase-negative staphylococci; IV, intravenous.

1. Tong SYC, et al. *Clin Microbiol Rev*. 2015; 28(3): 603-661. 2. Becker K, et al. *Clin Microbiol Rev*. 2014;27(4):870-926.

An AMR priority

S. aureus is a WHO & CDC high priority AMR pathogen



AMR, antimicrobial resistance; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

1. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017.
2. CDC Antibiotic resistance threats in the United States, 2019.

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A leading cause of mortality

MRSA is a leading pathogen for deaths attributed to AMR

WORLD	**26%**	In the high-income super-region, 26% of deaths attributable to AMR are due to *S. aureus*[1]
USA	**42%**	The rate of methicillin resistance among *S. aureus* clinical isolates from USA hospitals is 42.2%[2]
CHINA	**45%**	The rate of methicillin resistance among *S. aureus* clinical isolates in China is 44.6%[3]
EUROPE	**1–49%**	In European centers, rate of methicillin resistance among *S. aureus* vary from 1.4% in Netherlands to 49.1% in Cyprus[4]

AMR, antimicrobial resistance; MRSA, methicillin-resistant *Staphylococcus aureus*.

1. Antimicrobial Resistance Collaborators. *Lancet*. 2022;399(10325):629-655. 2. Sader HS, et al. *Antimicrob Agents Chemother*. 2017;61(9):e01043-17. 3. Hu F-P, et al. *Clin Microbiol Infect*. 2016;22 Suppl 1:S9-14. 4. WHO Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022 – 2020 data.

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Growing recognition of clinical significance

High rates of methicillin resistance among CoNS limits treatment options

	OR: 3.88	CoNS resistance is a strong predictor of in-hospital mortality[1]
USA	**57%**	The rate of methicillin resistance among CoNS clinical isolates from USA hospitals is 57.1%[2]
CHINA	**70%**	The rate of methicillin resistance among CoNS clinical isolates in China is 70.2%[3]
EUROPE	**65%**	The rate of methicillin resistance among CoNS clinical isolates from hospitals in Europe is 64.6%[2]

CoNS, coagulase-negative staphylococci; OR, odds ratio.

1. Obolski U, et al. *J Antimicrob Chemother*. 2014;69(9):2541-2546. 2. Sader HS, et al. *J Glob Antimicrob Resist*. 2021;24:48-52.
3. Ye Y, et al. *Microbiol Spectr*. 2022;10(1):e0146221.

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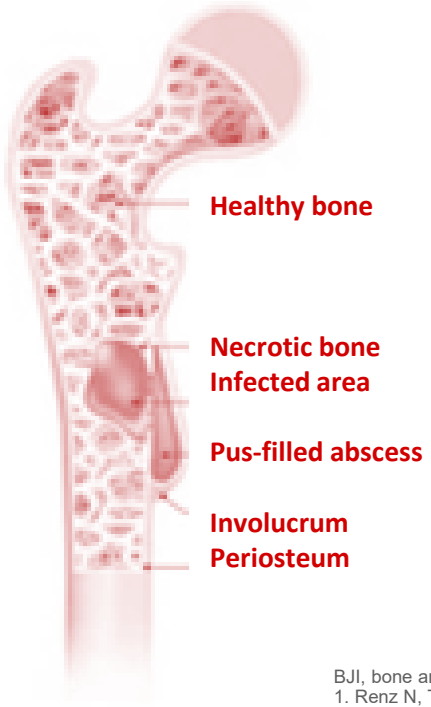
A major clinical challenge

Bone and joint infections (BJIs) are difficult to cure



Osteomyelitis	Prosthetic joint infection (PJI)	Septic arthritis

- Most commonly caused by **Staphylococci *(S. aureus and CoNS)***[1,2]
- Treatment requires long-term antibiotic treatment, usually combined with appropriate surgery[1]
- Limited robust clinical trial data for therapeutic options[1,2]
- In the OVIVA study, appropriately selected oral antibiotic therapy was noninferior to intravenous therapy when used during the first 6 weeks in the management of BJIs[3]
- Staphylococcal osteomyelitis is a major clinical challenge, with recurrent and persistent infections occurring in ~40% of patients[2]

"Toxicity of most current antibiotics is a problem. Quite a lot of side effects are seen after 3 weeks of treatment, necessitating a change in antibiotic treatment in about 30% of patients."
EU PJI Expert, 2021

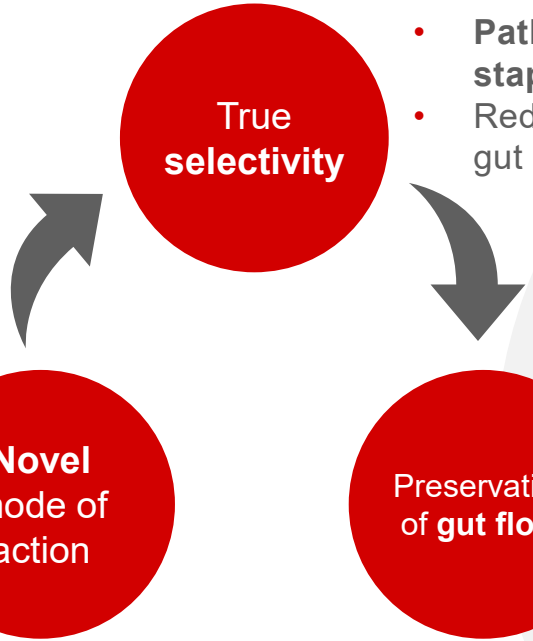
BJI, bone and joint infection; CoNS, coagulase-negative staphylococci.
1. Renz N, Trampuz A. Bone and Joint Infections. In: Evidence-Based Infectious Diseases, Third Edition, Eds. Dominik Mertz, Fiona Smaill, Nick Daneman. 2018. 2. Kavanagh N, et al. *Clin Microbiol Rev*. 2018;31:e00084-17. 3. Li H-K, et al. *N Engl J Med*. 2019;380(5):425-436.

Our answer

A pathogen-specific antibiotic against hard-to-treat *Staphylococcus* infections

Debiopharm vision

A three-point approach to tackling AMR



- **Pathogen-specific activity against staphylococci**
- Reduced off-target selection pressure on gut microbiota

Avoid dysbiosis and potential for superinfection by commensal organisms (e.g. *C. difficile*)

No cross resistance to any antibiotic classes

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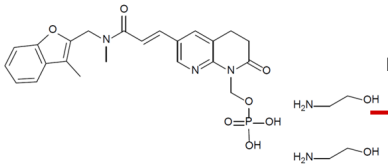
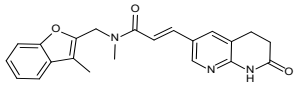
Novel mode of action

Afabicin: a first-in-class, *Staphylococcus*-specific antibiotic[1,2]

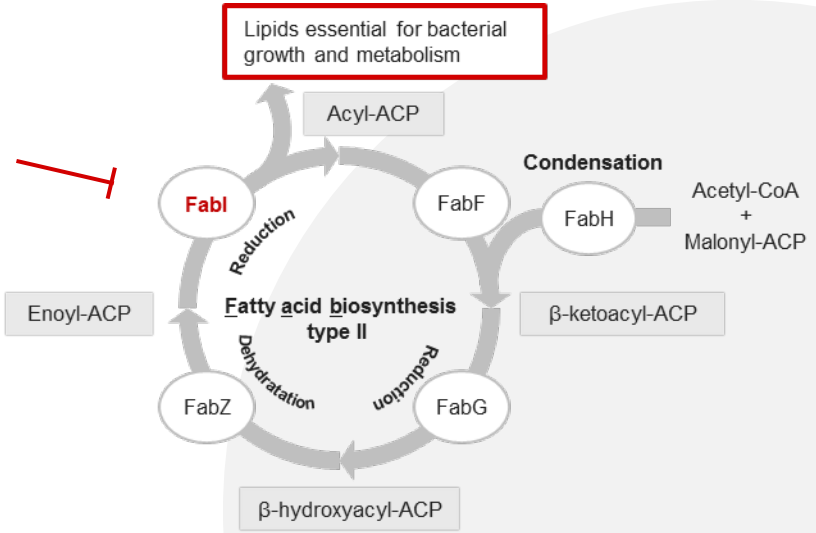


IV/oral afabicin
(prodrug)

Rapid *in vivo* conversion



Debio 1452
(active moiety)



Disruption of the bacterial fatty acid biosynthetic pathway preventing bacterial growth

- **In staphylococci, FabI is essential** to providing fatty acids for virtually all metabolic and structural needs
- When FabI is blocked, the structural integrity is lost, energy metabolism and protein metabolism is shut down

"Activity against both Staph. aureus and coagulase-negative staphylococci (including resistant strains) is a key advantage of uptake of afabicin."

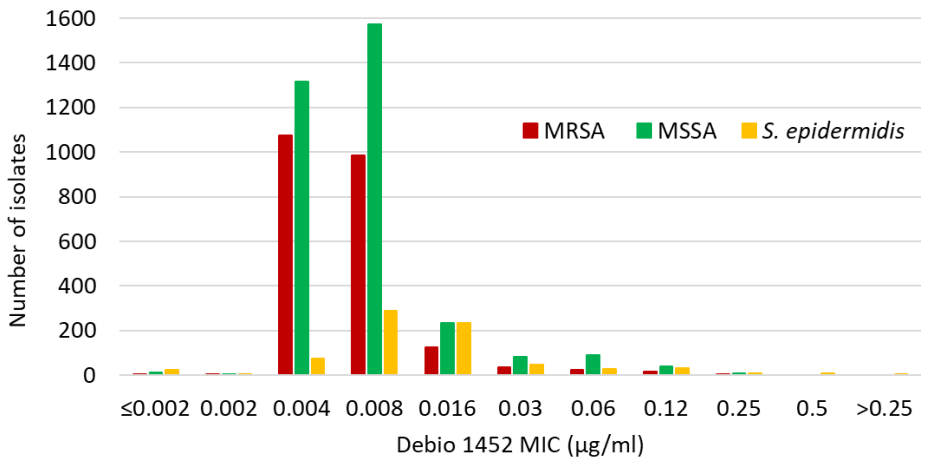
EU PJI Expert, 2021

1. Kaplan N, et al. *Antimicrob Agents Chemother.* 2012;56:5865-5874.
2. Nowakowska J, et al. Presented at Microbiome R&D and Business Collaboration Forum 2017; Presentation 10.

True selectivity

High selectivity and potency against staphylococci with various AMR profiles

MIC distribution for staphylococcal isolates (n=8,026)[1]



Bacterial Group/Genus	No. of Strains	MIC (µg/mL)		
		Range	MIC_{50}	MIC_{90}
Staphylococci				
S. aureus	7,135	≤0.001 - 0.25	≤0.008	0.016
S. epidermidis	891	≤0.001 - 0.5	0.008	0.06
S. lugdunensis	65	0.002 - >0.25	0.008	0.016
Other Gram-positive cocci				
Streptococcus	648	4 - >4	>4	>4
Enterococcus	1,056	1 - >4	>1	>4
Gram-negative non-fermenters				
Acinetobacter	38	>4	>4	>4
Moraxella	70	2 - >4	>4	>4
Pseudomonas	510	>4	>4	>4
Gram-negative fermenters				
E. coli & P. mirabilis	1,852	0.5 - >4	4	>4
Other Enterobacteriaceae	1,036	1 - >4	>4	>4
Gram-positive anaerobes				
various species	20	>8	>8	>8
Gram-negative anaerobes				
various species	19	>8	>8	>8

2004 – 2016 surveillance studies

- **Pathogen-specific activity against staphylococci**
- **Non-staphylococcal MIC_{90} >4 mg/mL**[1,2,3]
- **Low propensity for spontaneous resistance development in *S. aureus* and *S. epidermidis***[3]
- **No cross-resistance:** similar potency against MRSA, VISA, VRSA, LRSA, etc.[1,2,3]

AMR, antimicrobial resistance; CoNS, coagulase-negative staphylococci; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; VISA, vancomycin-intermediate *S. aureus*, VRSA, vancomycin-resistant *S. aureus*; LRSA, linezolid-resistant *S. aureus*.

1. Hawser S, et al. Presented at ECCMID 2018; Poster 1824; 2. Kaplan N, et al. *Antimicrob Agents Chemother.* 2012;56:5865-5874. 3. Debiopharm International. Data on file.

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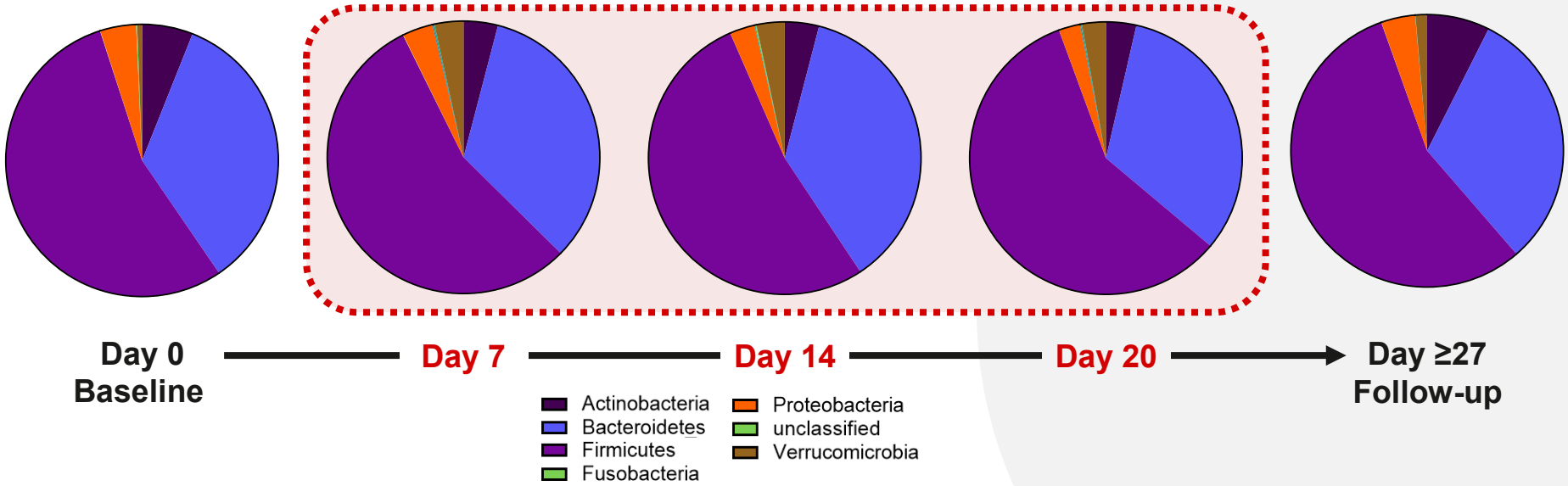
Preservation of gut flora

Afabicin preserves composition of human gut microbiota, even with prolonged treatment

Mean relative abundance (%) at the phylum level in human stool samples (n=15)



Nowakowska J, et al. Presented at ECCMID 2018; Poster 0281.

Debiopharm's answer

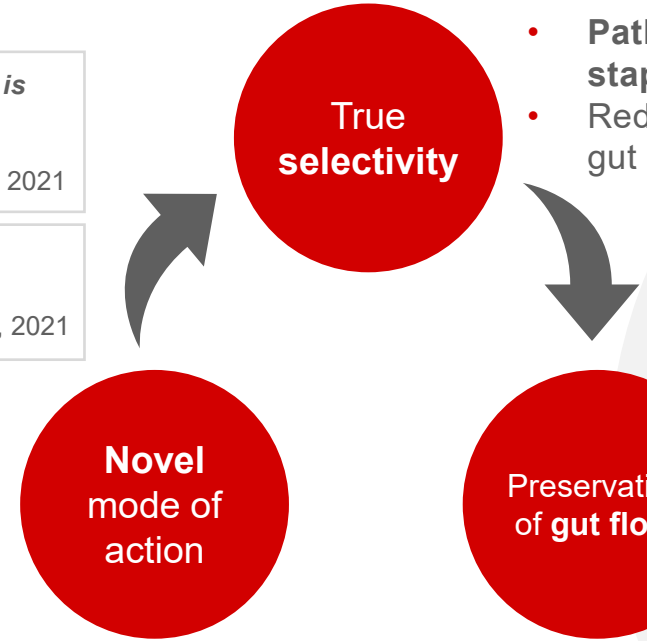
Pathogen-specific afabicin brings a new IV & oral paradigm to antibiotic therapy

"The lack of impact on the microbiome is the most important differentiator for afabicin"

US PJI Expert, 2021

"Pill instead of PICC line – this is attractive."

US ID specialist, 2021



- **Pathogen-specific activity against staphylococci**
- Reduced off-target selection pressure on gut microbiota

Avoid dysbiosis and potential for superinfection by commensal organisms (e.g. *C. difficile*)

No cross resistance to any antibiotic classes

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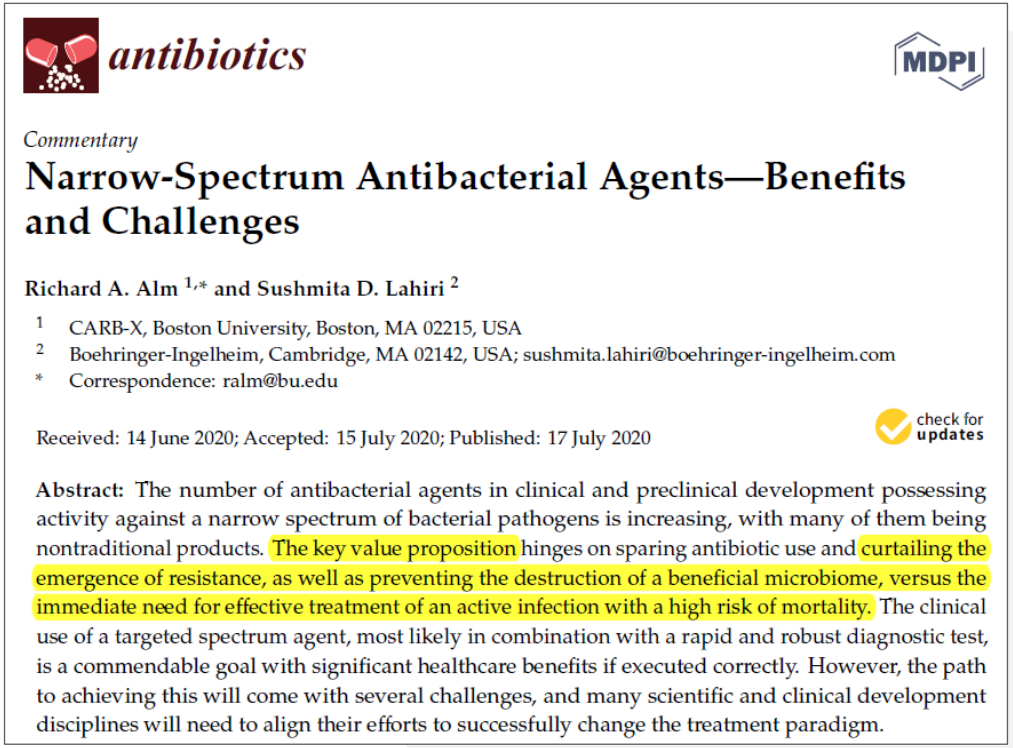
Our value proposition

A Phase III-ready medication, with open registration paths to multiple hard-to-treat indications

A new positioning paradigm to combat AMR

Pathogen-specific antibiotics have a more impactful value proposition

- Unlike conventional narrow spectrum antibiotics, **novel pathogen-specific antibiotics** can:
  - ✓ Treat active infection, ***and***
  - ✓ Prevent the destruction of beneficial microbiome[1]
- **Targeted, microbiota-sparing antibiotics** should not be kept in reserve[2]
  - ✓ Help control antibiotic resistance



antibiotics

MDPI

Commentary

Narrow-Spectrum Antibacterial Agents—Benefits and Challenges

Richard A. Alm [1,*] and Sushmita D. Lahiri [2]

[1] CARB-X, Boston University, Boston, MA 02215, USA
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check for updates

Abstract: The number of antibacterial agents in clinical and preclinical development possessing activity against a narrow spectrum of bacterial pathogens is increasing, with many of them being nontraditional products. The key value proposition hinges on sparing antibiotic use and curtailing the emergence of resistance, as well as preventing the destruction of a beneficial microbiome, versus the immediate need for effective treatment of an active infection with a high risk of mortality. The clinical use of a targeted spectrum agent, most likely in combination with a rapid and robust diagnostic test, is a commendable goal with significant healthcare benefits if executed correctly. However, the path to achieving this will come with several challenges, and many scientific and clinical development disciplines will need to align their efforts to successfully change the treatment paradigm.

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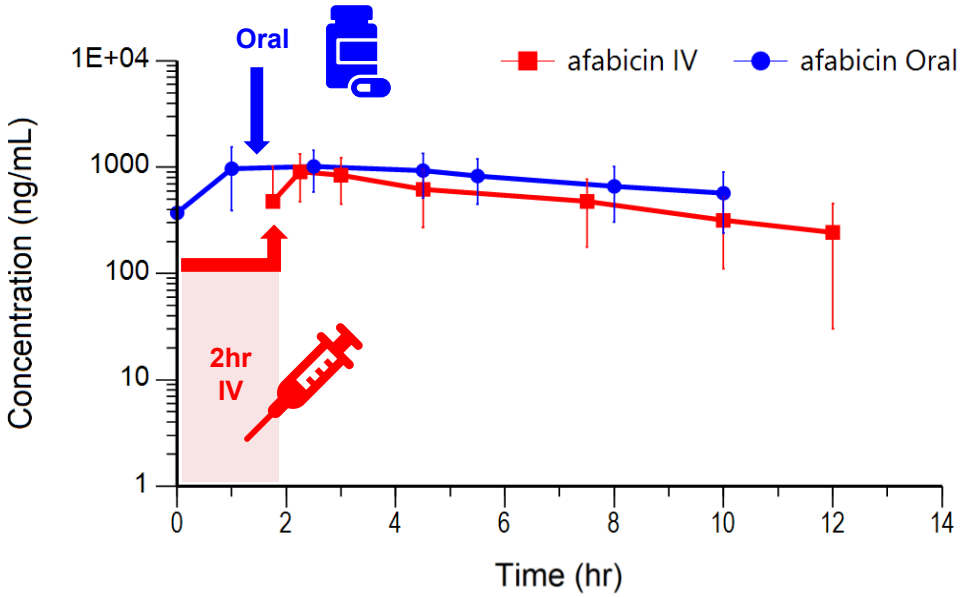
1. Alm RA, Lahiri SD. *Antibiotics*. 2020;9(7):418; 2. Diamantis S, et al. *Antibiotics*. 2022;11(7):924

Bioavailability

Equivalent exposure with oral and IV afabicin

- Rapid conversion of the prodrug afabicin into the active moiety afabicin desphosphono after administration
- Half life 7-12 hours
- **Oral bioavailability ~70%**
- No significant food effect
- High tissue distribution

Mean PK profiles for afabicin 55 mg IV BID and 80 mg oral BID*



*Data from Phase 2 study Debio 1450-BJI-205 cohort 1B: IV treatment assessed at Day 1 (n=15); oral treatment assessed at end of treatment (n=13).
BID, twice a day; IV, intravenous.
Debiopharm International. Data on file.

Positive
Phase II study

Afabicin displays similar efficacy to vancomycin and linezolid in ABSSSI

Phase II study, in the US[1]

- 330 patients with ABSSSI
- Randomized double-blind
- Vancomycin/linezolid as control

Results

- Study objectives were met
- Demonstrated efficacy even in strains resistant to other antibiotics
- Well tolerated treatment
- Good results in cellulitis and diabetes mellitus

	Afabicin 80mg/120mg BID	Afabicin 160mg/240mg BID	Vancomycin 1g, Linezolid 600mg BID	Overall
Patients (n)	92	91	101	284
Responders (n)	87	82	92	261
Non-responders (n)	5	9	9	23
ECRR (%)	**94.6**	**90.1**	**91.1**	**91.9**

"With afabicin you can do IV and oral regimens with the same drug. This is simple, and both patients and healthcare providers like this. Switching to a different drug gives you a higher risk of side effects."

US ID Specialist, 2021

Efficacy of active moiety demonstrated in another ABSSSI Phase IIa, open-label study (published success rate >93%).[2]

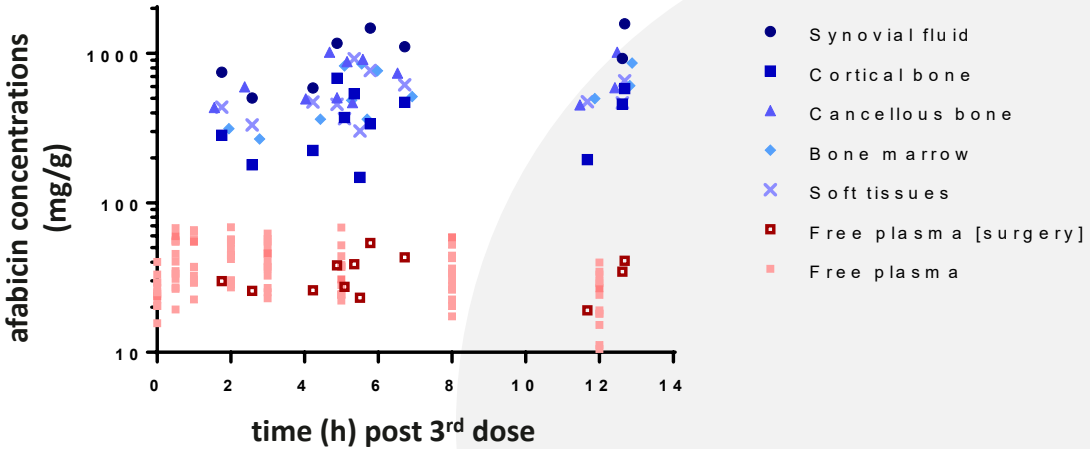
ABSSSI, acute bacterial skin and skin structure infection; BID, twice a day; ECRR, Early Clinical Response Rate.

1. Wittke F, et al. *Antimicrob Agents Chemother.* 2020;64(10):e00250-20. 2. Hafkin B, et al. *Antimicrob Agents Chemother.* 2015;60(3):1695-1701.

Bone penetration

High penetration of the afabicin active moiety in bone tissues

14 patients undergoing hip replacement surgery following three oral dose of 240 mg afabicin



"You need to get antibiotics to site of infection and you need adequate penetration into bone"

EU DFO Expert, 2021

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Menetrey A, et al. *Antimicrob Agents Chemother.* 2019;63(3):e01669-18.

Phase II study in BJIs

Ongoing afabicin Phase II study in bone & joint infections (BJIs)

Overview

- **Multi-center, international, open-label study**
- **BJIs:** septic arthritis, osteomyelitis, prosthetic joint infections
- **Up to 96 patients**

Study objectives & current results

- **Safety after long treatment duration**
- **Efficacy (Day 8, End of treatment, 1 and 3 months follow-up)**
- **Currently all patients who have reached end of treatment visit are responders**

> ***"There is nobody else in that space (BJI). Take it!"***
>
> **US Podiatrist, 2021**

> ***"Effective against MRSA but less dangerous than vancomycin, we are happy."***
>
> **EU PJI Expert, 2021**

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BJI, bone and joint infection; FPFV, first patient first visit.
ClinicalTrials.gov. NCT03723551

Regulatory & IP opportunities

EXPECTED TIME TO MARKET IN BJI

2030

DATA/MARKET EXCLUSIVITY

2040

US: New Chemical Entity data exclusivity & QIDP
EU: New Chemical Entity data exclusivity

PATENT PROTECTION
Compound 2038 (2033+5)
Or
DFO 2042 (2037+5)

US DESIGNATIONS

Qualified infectious disease product (**QIDP**) fast-track in osteomyelitis and ABSSSI (**FDA**)

EU DESIGNATIONS

Orphan drug designation (**ODD**) for osteomyelitis in Europe

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Product Highlights

First-in-class, pathogen-specific afabicin is pioneering in hard-to-treat BJI

Strongly differentiated, pathogen-specific compound with significant value potential in BJI and beyond

- **Novel MoA:** disruption of the bacterial fatty acid biosynthetic pathway preventing bacterial growth
- First FabI inhibitor with **highly selective *Staphylococcus*-specific *in vitro* activity** against all staphylococcal species. Inactive against non-staphylococcal pathogens causing BJI in humans
- Low off-target selection pressure on human microbiota and **preservation of gut flora**
- **Low propensity for emergence of resistance** and no cross-resistance with other antibiotics
- **High bone penetration**
- High oral bioavailability allowing **easy switch from IV to oral form**
- Positive Phase II results in ABSSSI (n=330)
- Ongoing Phase II study in BJI

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ABSSSI, acute bacterial skin and skin structure infection; BJI, bone and joint infection; IV, intravenous; MoA, mechanism of action.

Contact informations

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