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Procalcitonin (PCT)

Antibiotic Stewardship implementation Guide

Part 1: The Importance of ABS

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Content

This guide is the first of a three-part series on Antibiotic stewardship and focuses on the importance of practicing antibiotic stewardship. To learn more about implementing and optimizing an Antibiotic Stewardship program in your hospital be sure to check out part two and part three in the series.

Purpose of this booklet

Evidence from around the world shows a global decline in the effectiveness of antibiotics. Inappropriate use of antibiotics has driven the dramatic increase in resistance seen to all first-line and last-resort antibiotics. Antimicrobial resistance (AMR) has been identified by the WHO as a global healthcare threat as it limits our capacity to fight life-threatening diseases.

Antibiotic stewardship (ABS) is a key strategy used to preserve the effectiveness of antibiotics by promoting and monitoring their responsible use. If used effectively, it can help reduce and optimize the prescription of antibiotics in several healthcare settings.

This booklet serves as a practical guide to support the implementation of an ABS program within a hospital, outlining the key steps needed for successful implementation. Most of the information on ABS implementation have been adopted from recommendations and guidelines from IDSA[1], CDC[2], WHO[3], BSAC[4], and CDDEP.[5] The role of in-vitro diagnostics in an ABS program is discussed, and in particular the role of the biomarker procalcitonin (PCT) is highlighted, as the WHO recognizes the value of PCT for tertiary care facilities and above “to guide antibiotic therapy or its discontinuation in sepsis and lower respiratory tract infection”.[6]

We gratefully acknowledge the help of Dr. Broyles, Prof. Kwa and Prof. Giamarellos-Bourboulis for providing the examples for practical implementations of procalcitonin into an antibiotic stewardship program.

Antibiotic stewardship – quality management for antibiotic treatment

Antibiotics are a double-edged sword. They have saved probably millions of lives since their introduction to medicine. However, antibiotics can cause toxicity, potential harmful drug-drug interactions and can severely disturb the microbiome (Figure 1). Over the last decades, we have learned that if antibiotic therapy is used when it is not indicated or if it is used for too long or too broadly, then we not only select for resistance but may also increase mortality.

This causes a clinical dilemma: if we withhold antibiotics, or if we do not target the underlying pathogen, we put patients at risk – particularly in sepsis. On the other hand, data show that non-specific rapid administration of broad-spectrum antibiotics increases mortality.[8] The ideal approach is early targeted treatment. However, that is not possible in many patients because the underlying pathogen cannot be identified, particularly during the first couple of days of infection.

The solution to this problem is called "antibiotic stewardship" (ABS). ABS can be understood as a quality management tool for antibiotic prescription and administration and includes a regular and structured evaluation of antibiotic treatment. ABS includes two levels: a general hospital-based level, i.e. implementation of an ABS program, and an individual patient-centered

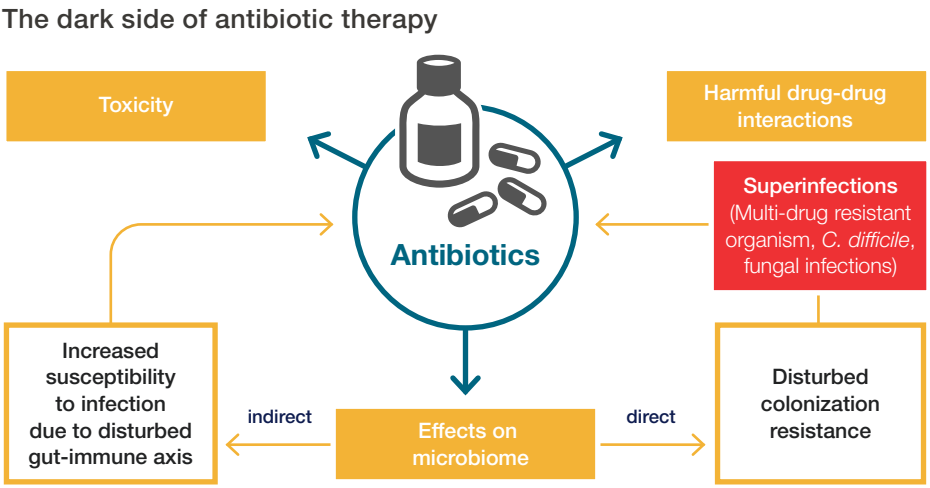

Figure 1. The dark side of antibiotic therapy (adapted from Pletz M, Der Klinikarzt 2019)[7]

one, i.e. right drug, right time, right dosage and right duration.

This booklet addresses both facets of ABS and compiles the major evidence for ABS, including the most recent studies. It provides practical advice on how to create an ABS team and an ABS program and how to implement ABS principles into daily clinical routine. Among these, the aid of biomarkers in treatment decisions is one helpful strategy.

Procalcitonin (PCT) is not the only biomarker used to aid antibiotic treatment decisions but it is currently the most extensively studied. It can help make the decision to start or withhold antibiotics, particularly in the emergency department for patients with mild respiratory tract infections. There are also many studies that show PCT can help to shorten the duration of antibiotic treatment.

Since no biomarker is perfect, PCT must not replace clinical judgement but it may add to it. The limitations of PCT have to be taken into account and it must not be used to shorten antibiotic treatment below the minimal duration according to the specific guidelines for specific infections.

However, in the right context, PCT-aided shortening of antibiotic treatment duration may even decrease mortality as shown in a major cluster randomized controlled trial.[9]

This booklet can be a guide for establishing an effective ABS program. Several leading scientists in the field, who have contributed to this booklet, can guarantee its quality. I hope this booklet is widely distributed to help antibiotics be used as they should: "As much as needed and as little as necessary."

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Professor Pletz leads a clinical research group focusing on novel diagnostic and therapeutic strategies against multi-drug resistant (MDR) bacterial pathogens. He has published more than 300 peer-reviewed papers on respiratory infections, sepsis, antimicrobial resistance, and antibiotic stewardship and serves on the editorial board of CHEST, Clinical Infectious Diseases and Infection. He has received numerous scientific awards.

He is the president of Paul Ehrlich Society for Chemotherapy, the Deputy Director of the German CAPNETZ, and a scientific advisor for the German Robert Koch Institute and the WHO. He acts on the steering committee of the National Research Program "Antimicrobial Resistance" (NRP 72) funded by the Swiss National Foundation.

Why antibiotic stewardship in the hospital is important

1

1.1 Antibiotic overuse leads to resistance developing

It is estimated that **one-third of all antibiotics prescribed in high-income countries are likely to be unnecessary**. For the remaining two-thirds there are opportunities to optimize drug selection, dose, and duration to reduce total antibiotic use (Figure 2).

Antibiotic use is rising globally due to persistently high prescribing rates in high-income countries, combined with a continued increase in rates in middle- and low-income countries (Figure 3).

The overuse and misuse of antibiotics in both humans and animals accelerate the natural process of antimicrobial resistance by selecting for resistant strains. Inadequate infection prevention and control in hospitals and clinics promotes the spread of resistant bacteria. This has led to **increased resistance to life-saving antibiotics around the world**, greatly reducing treatment options. Some bacterial strains have become resistant to many first- and second-line antibiotics. These multidrug-resistant (MDR) strains can only be treated with last-resort antibiotics, if they can be treated at all (Figure 4).

As new antibiotics show only limited effectiveness against resistant strains, and there is a lack of new antibiotics being brought to market,[11] it is vital to control resistance rates to current antibiotics so infections in the future can also be fought effectively.

Figure 2. Antibiotic prescriptions in US doctors' offices and emergency departments (adapted from CDC. Antibiotic Use in the United States, 2018 Update, 2019)[10]

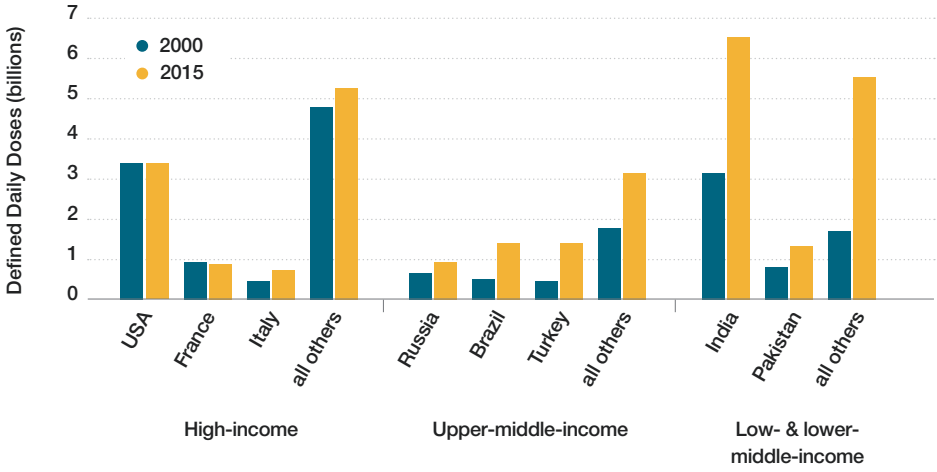

Figure 3. Antibiotic prescription in billion defined daily dose per country in 2000 and 2015 (adapted from Klein EY et al., PNAS 2018)[12]

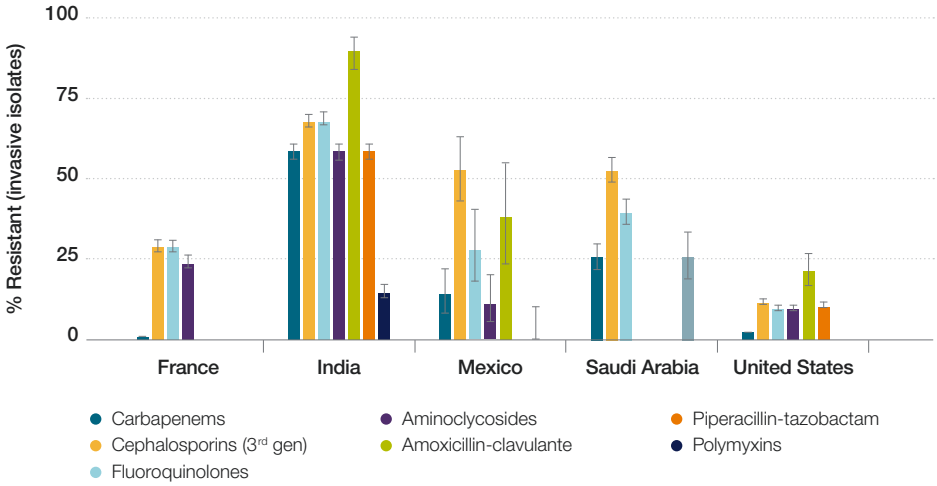

Figure 4. Antibiotic resistance of *Klebsiella pneumonia* in selected countries (adapted from CDDEP Resistance Map: Antibiotic resistance, Oct 2020)[13]

1.2 Antibiotic resistance-related patient outcomes

A growing number of infections, such as pneumonia, tuberculosis, gonorrhea, and salmonellosis, are becoming harder to treat as the antibiotics used to treat them become less effective due to resistance. This means that as clinicians need to prescribe more second- and third-line antibiotics to treat common infections, there is a risk of resistance for these reserve antibiotics developing. Inadequate therapy leads to increased mortality and morbidity and increases adverse events such as infection with *Clostridioides difficile* (Figure 5).

Antibiotic resistance disproportionately affects certain risk-groups. The burden of infections due to antibiotic-resistant bacteria was highest in infants (aged <1 years) and people aged 65 years or older.[15]

	European Union Population 450m	**United States*** Population 300m	
	Antibiotic resistant bacteria cause ...**	**Antibiotic resistant bacteria and fungi cause ...****	**Infections related to Clostridioides difficile*****
	**>670,000** **infections**	**2,868,700** **infections**	**223,900** **cases**
	**>33,000** **deaths**	**35,900** **deaths**	**12,800** **deaths**
	>74.000 **loss in DALYs**	**$ 5.75 billion** **direct costs**	

Figure 5. Annual number of infections with antibiotic-resistant microorganisms, and related deaths, DALYs (Daily Adjusted Life-Years) and societal costs, in EU and US (adapted from CDC. Antibiotic Resistance Threats in the United States, 2019, and Cassini et al., Lancet Infectious Disease 2019)[14,15]

* National burden reflects de-duplicated infection and death estimates
** Minimum annual estimate
*** *Clostridioides difficile* cases from hospitalized patients in 2017

1.3 Antibiotic stewardship is a key strategy used to overcome antibiotic resistance

ABS is one pillar that contributes to the fight against antibiotic resistance, including MDR, which has been shown to be highly effective. In a recent meta-analysis including more than 9 million patients, ABS programs significantly reduced the incidence of infection and colonization with MDR gram-negative bacteria and *Clostridioides difficile* infections in hospitalized patients.[16]

However, ABS should be part of a wider strategy to reduce antibiotic resistance (Figure 6).

Figure 6. Strategies needed in national antibiotics policies (adapted from CDDEP 2015 State of the world's antibiotics 2015)[5]

1.4 Key messages

Antibiotic resistance is a major global healthcare threat as a growing number of infections are becoming harder and more expensive to treat. This leads to increased mortality, morbidity and numbers of adverse events, especially in vulnerable populations such as infants and the elderly.

Antibiotic stewardship is an effective tool to fight AMR to ensure "the right antibiotic for the right patient, at the right time, with the right dose, the right route and cause the least harm to the patient and future patients". [4]

Effective ABS can help …

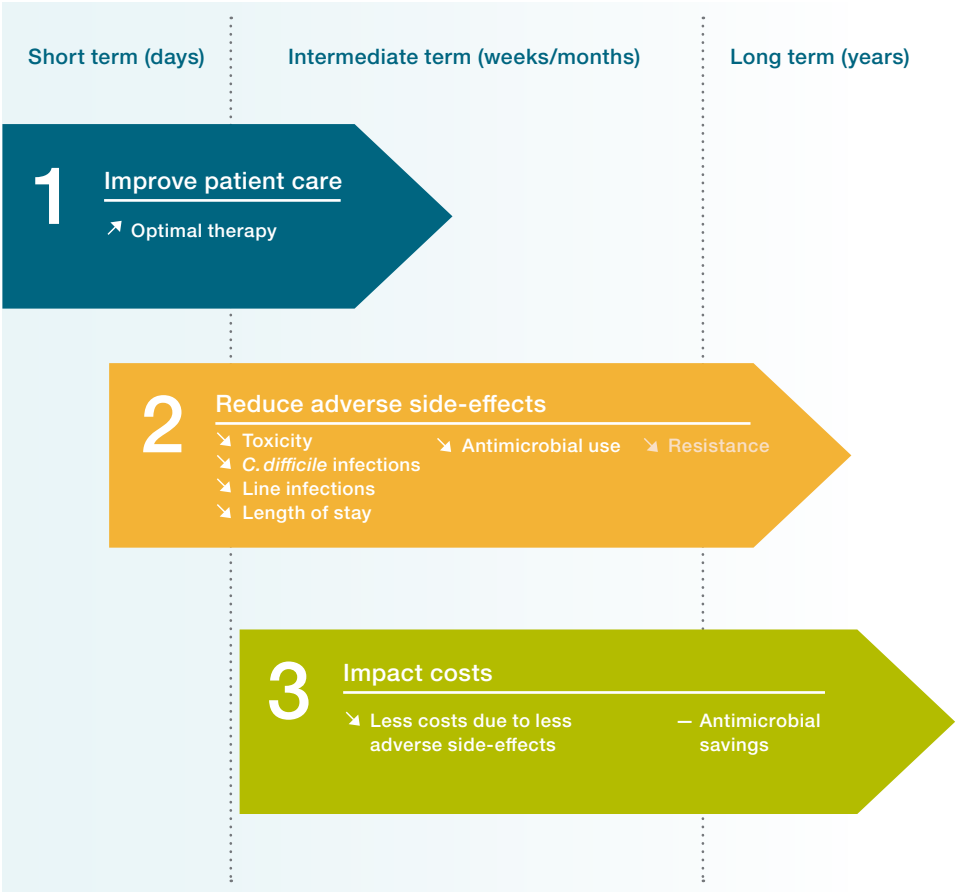

Figure 7. Impact of antibiotic stewardship (adapted from Dik et al., Expert review of Anti-infective Therapy 2016)[17]

References

Please note, this guide is part one in a three-part series. The references below are a culmination of the references for all three guides in the series.

1. Barlam TF et al., Clinical Infectious Diseases 2016; 62(10): e51-e77 IDSA Guideline. https://doi.org/10.1093/cid/ciw118
2. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at https://www.cdc.gov/antibiotic-use/core-elements/hospital.html. Date of access: 08.11.2021
3. WHO Competency Framework for Health Workers' Education and Training on Antimicrobial Resistance. Geneva: World Health Organization; 2018 (WHO/HIS/HWF/AMR/2018.1). License: CC BY-NC-SA 3.0 IGO. Available at https://www.who.int/publications/i/item/who-competency-framework-for-health-workers%E2%80%99-education-and-training-on-antimicrobial-resistance. Date of access: 08.11.2021
4. BSAC. Antimicrobial Stewardship: From Principles to Practice – eBook 2018. Available at https://bsac.org.uk/antimicrobial-stewardship-from-principles-to-practice-e-book/. Date of access: 08.11.2021
5. CDDEP. 2015 The State of the World's Antibiotics, 2015. CDDEP: Washington, D.C. Available at https://cddep.org/publications/state_worlds_antibiotics_2015/. Date of access: 08.11.2021
6. World Health Organization (2021). The selection and use of essential in vitro diagnostics: report of the third meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2020 (including the third WHO model list of essential in vitro diagnostics). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1031). License: CC BY-NC-SA 3.0 IGO. Available at: https://apps.who.int/iris/handle/10665/339064/. Date of access: 08.11.2021
7. Pletz M, Der Klinikarzt 2019; 48(11): 454-455. https://doi.org/10.1055/a-1020-1071
8. Schuts EC et al., Lancet Infect Dis 2016; 16: 847-856. https://doi.org/10.1016/s1473-3099(16)00065-7
9. de Jong E et al., Lancet Infect Dis 2016; 16 (7): 819-827. https://doi.org/10.1016/S1473-3099(16)00053-0
10. CDC. Antibiotic Use in the United States, 2018 Update: Progress and Opportunities. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at https://www.cdc.gov/antibiotic-use/stewardship-report/pdf/stewardship-report-2018-508.pdf. Date of access: 08.11.2021
11. 2019 antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO. Available at https://apps.who.int/iris/handle/10665/330420. Date of access: 08.11.2021
12. Klein EY et al., PNAS 2018; 115:15:E3463-E3470. https://doi.org/10.1073/pnas.1717295115
13. CDDEP. Resistance Map: Antibiotic resistance. Available at https://resistancemap.cddep.org/AntibioticResistance.php. Date of access: 08.11.2021
14. CDC. Antibiotic Threats in the United States, 2019 Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019. https://dx.doi.org/10.15620/cdc:82532
15. Cassini A et al., Lancet Infect Dis 2019; 19: 56-66. https://doi.org/10.1016/S1473-3099(18)30605-4
16. Baur D et al., Lancet Infect Dis 2017; 17: 990-1001. https://doi.org/10.1016/S1473-3099(17)30325-0

17. Dik JWH et al. Expert Review of anti-infective therapy 2016, 14(6): 569-575. https://doi.org/10.1080/14787210.2016.1178064

18. Public Health England, Antimicrobial prescribing and stewardship competencies, Online October 2013. Available at https://www.gov.uk/government/publications/antimicrobial-prescribing-and-stewardship-competencies. Date of access: 08.11.2021

19. Chung GW et al., Virulence 2013; 4(2): 151-157. https://doi.org/10.4161/viru.21626

20. Loo LW et al., International Journal of Antimicrobial Agents 2019; 53: 606-611. https://doi.org/10.1016/j.ijantimicag.2019.01.008

21. Plan, Do, Study, Act (PDSA) cycles and the model for improvement. Available at https://www.england.nhs.uk/wp-content/uploads/2021/03/qsir-plan-do-study-act.pdf. Date of access: 08.11.2021

22. Second WHO Model List of Essential In Vitro Diagnostics. Geneva: World Health Organization; 2019 (WHO/MVP/EMP/2019.05). License: CC BY-NC-SA 3.0 IGO. Available at https://www.who.int/publications/i/item/WHO-MVP-EMP-2019.05. Date of access: 08.11.2021

23. Hey J et al., Clin Chem Med Lab 2018: 56(8); 1200-1209. https://doi.org/10.1515/cclm-2018-0126

24. Wirz Y et al., Critical Care 2018; 22: 191. https://doi.org/10.1186/s13054-018-2125-7

25. Kyriazopoulou E et al., Am J Respir Crit Care Med 2020. https://doi.org/10.1164/rccm.202004-1201OC

26. Schuetz P et al., Clin Chem Lab Med 2019; 57(9): 1308-1318. https://doi.org/10.1515/cclm-2018-1181

27. Broyles MR et al., Open Forum Infect Dis 2017; 4(4): ofx213. https://doi.org/10.1093/ofid/ofx213

28. Voermans AM et al., OMICS A journal of integrative Biology (2019); 23(10): 508-515. https://doi.org/10.1089/omi.2019.0113

29. Schuetz P et al., Lancet Infect Dis 2018; 18 (1): 95-107. https://doi.org/10.1016/S1473-3099(17)30592-3

30. Hohn A et al., Infection 2015; 43(4): 405-412. https://doi.org/10.1007/s15010-014-0718-x

31. Stocker M et al. and the NeoPlnS Study Group, Lancet 2017; 390: 871-881. https://doi.org/10.1016/S0140-6736(17)31444-7

Want to learn more?

Find out more on ABS

BSAC https://bsac.org.uk/education/
CDC https://www.cdc.gov/antibiotic-use/healthcare/evidence.html
IDSA https://academy.idsociety.org/course-catalog-table?f%255B0%255D=field_course_format%3A19&f%5B0%5D=field_course_format%3A19
WHO https://www.who.int/activities/raising-awareness-and-educating-on-antimicrobial-resistance

Find out more on hospital ABS programs

CDC https://www.cdc.gov/antibiotic-use/training

Find out more on local resistance

CDDEP https://resistancemap.cddep.org/

Find out more on antimicrobial prescribing guidelines

NICE https://www.nice.org.uk/guidance/health-protection/communicable-diseases/antimicrobial-stewardship

Find out more on infection prevention and control

ECDC https://www.ecdc.europa.eu/en/publications-data/directory-guidance-prevention-and-control/training/training-courses-infection

Find out more on the use of procalcitonin in ABS

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