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Think antibiotic stewardship

A practical guide to the implementation of an antibiotic stewardship program in hospitals

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Content

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.

Introduction

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,

The dark side of antibiotic therapy

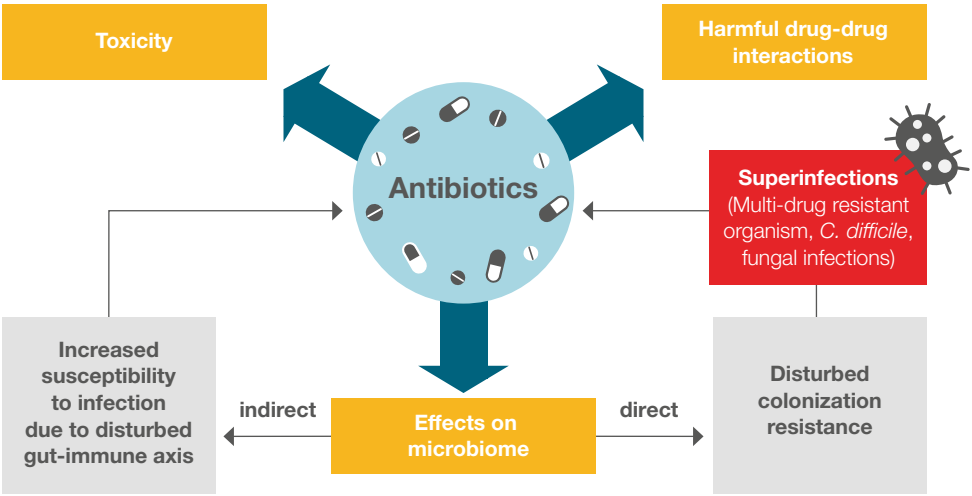


Figure 1 The dark side of antibiotic therapy (adapted from Pletz M, Der Klinikarzt 2019)[7]

i.e. implementation of an ABS program, and an individual patient-centered 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.”

Prof. Dr. med. Mathias W. Pletz

Prof. Dr. med. Mathias W. Pletz

Professor for Infectious Diseases and the funding chair of the Institute for Infectious Diseases and Infection Control of the University Hospital in Jena (Germany).

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 incoming president of the Paul-Ehrlich-Society for Anti-infective Therapy, 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.

Part 1 – Why implementation of antibiotic stewardship in the hospital is important

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.

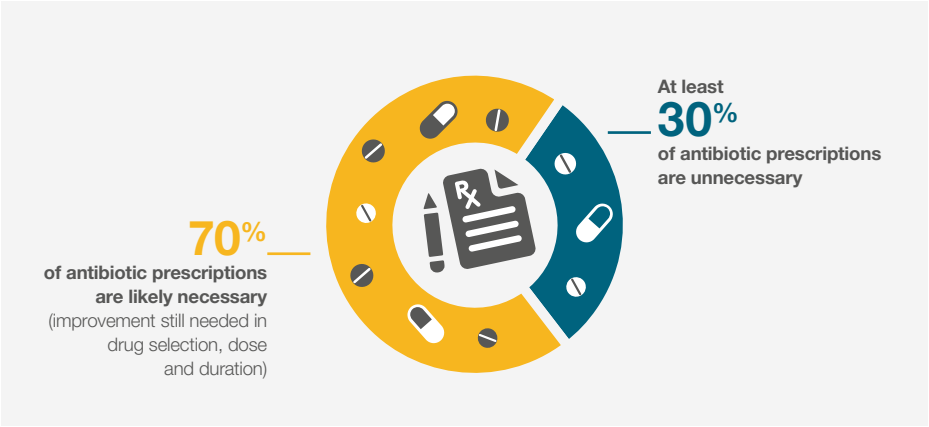


Figure 2 Antibiotic prescriptions in US doctors' offices and emergency departments (adapted from CDC. Antibiotic Use in the United States, 2018 Update, 2019)[10]

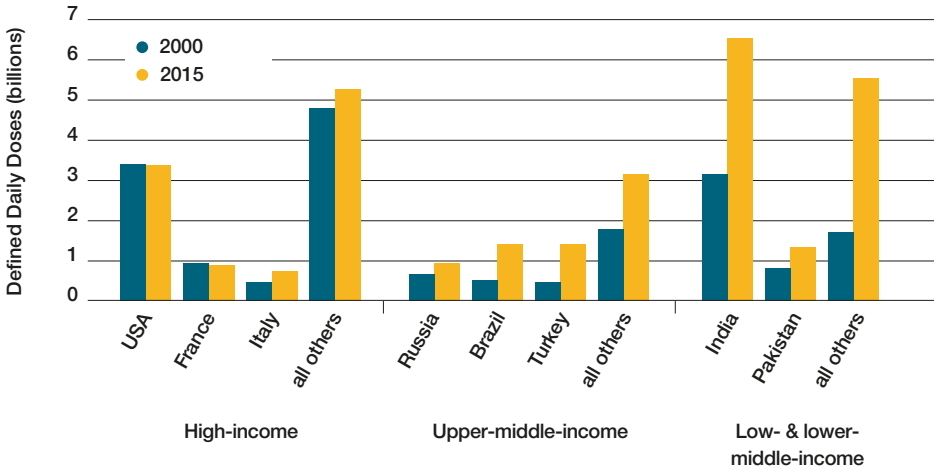


Figure 3 Antibiotic prescription in billion defined daily dose per country in 2000 and 2015 (adapted from Klein EY et al., PNAS 2018)[12]

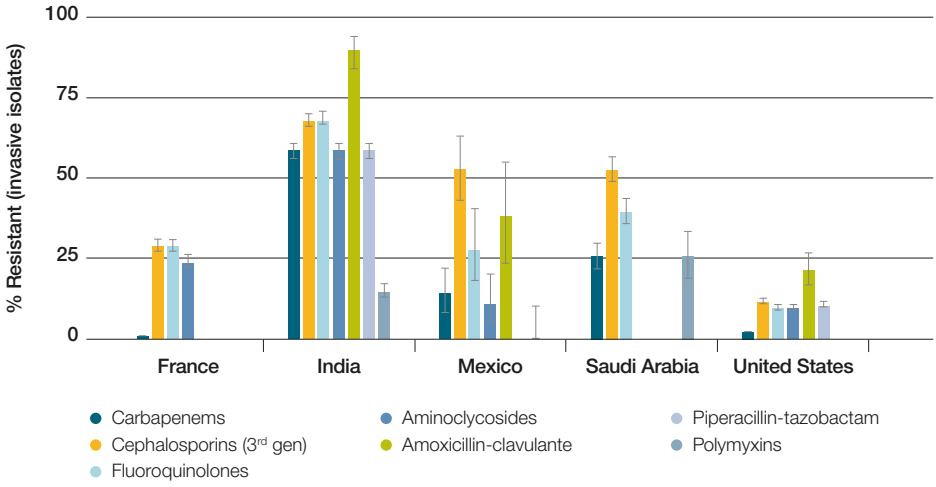


Figure 4 Antibiotic resistance of *Klebsiella pneumonia* in selected countries (adapted from CDDEP Resistance Map: Antibiotic resistance, Oct 2020)[13]

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).

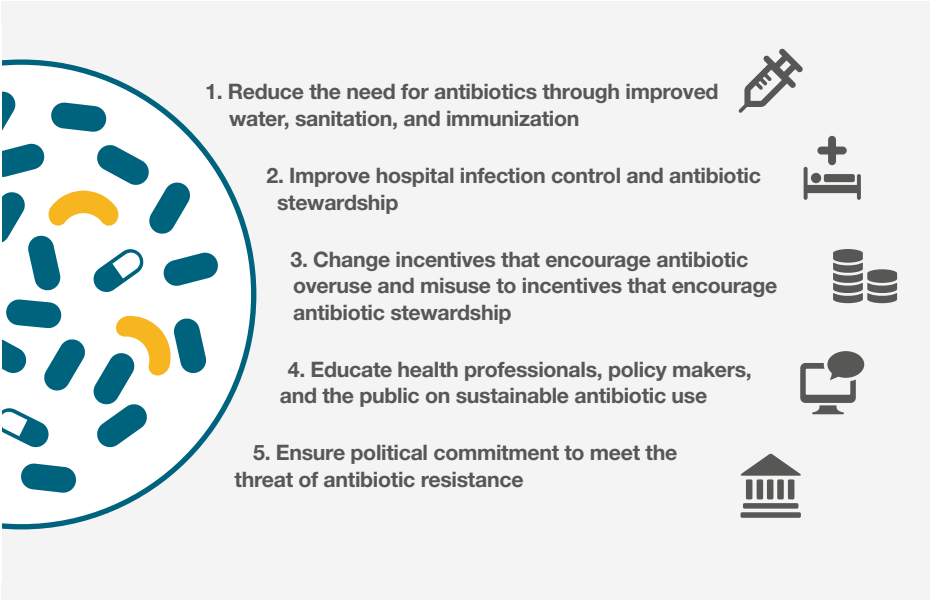


Figure 6 Strategies needed in national antibiotics policies (adapted from CDDEP 2015 State of the world's antibiotics 2015)[5]

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 …

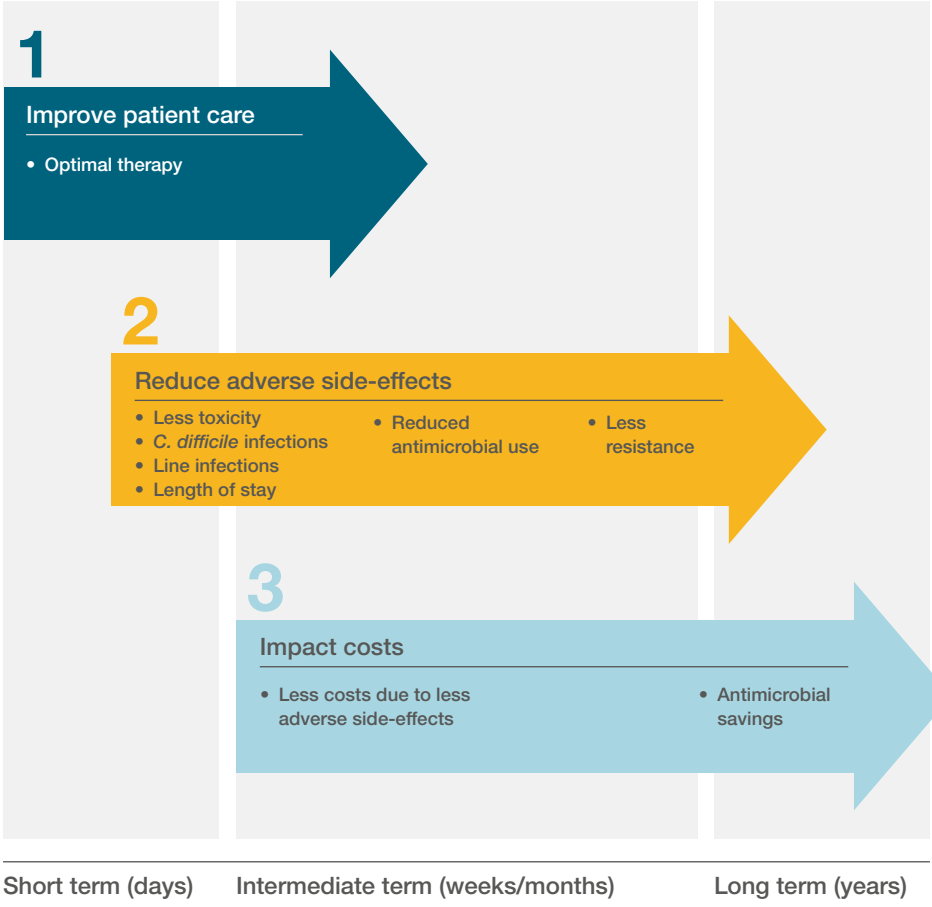


Figure 7 Impact of antibiotic stewardship (adapted from Dik et al., Expert review of Anti-infective Therapy 2016)[17]

Part 2 – How to implement an antibiotic stewardship program in the hospital

2.1 Core elements of antibiotic stewardship programs

There is no single template for an antibiotic stewardship program (ABS) that leads to optimal antibiotic prescribing. The complex medical decision-making surrounding antibiotic use and the differences in hospital size and care means programs are expected to differ. However, effective programs can still be implemented in different types of hospitals provided there is sustained commitment to the program. Strong support and leadership and a multidisciplinary approach are pivotal to success. The Centre for Disease Control and Prevention (CDC) has listed seven core elements that provide the framework for a successful ABS program (Figure 8).

Hospital leadership commitment

Dedicate necessary human, financial, and information technology resources.

Accountability

Appoint a leader or co-leaders, such as physician and pharmacist, responsible for program management and outcomes.

Pharmacy expertise

Appoint a pharmacist, ideally as the co-leader of the stewardship program, to help lead implementation efforts to improve antibiotic use.

Action

Implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use.

Tracking

Monitor antibiotic prescribing, impact of interventions, and other important outcomes, like *C. difficile* infections and resistance patterns.

Reporting

Regularly report information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership.

Education

Educate prescribers, pharmacists, nurses, and patients about adverse reactions from antibiotics, antibiotic resistance, and optimal prescribing.

Figure 8 Core elements of a hospital antibiotic stewardship program (adapted from CDC. Core Elements of Hospital Antibiotic Stewardship Programs. 2019)[2]

2.2 The antibiotic stewardship toolkit

2.2.1 Elements of the antibiotic stewardship toolkit

Within the framework of an ABS program, there are multiple interventions that could improve antibiotic decision making (Figure 9). When launching an ABS program, it is recommended that the core ABS interventions are implemented initially. Once the ABS program has been successfully established, additional strategies can be added as appropriate.

Core	Additional
Multidisciplinary ABS team ▸ page 19	**De-escalation of therapy based on culture results**
Guideline development ▸ page 20	**Dose optimization**
Formulary restriction with preauthorization of named anti-infectives ▸ page 22	**Intravenous (IV) to oral (PO) switch**
AND/OR	**Education** ▸ page 21
Prospective audit and feedback ▸ page 22	**Antimicrobial order forms**
	Antimicrobial cycling
	Combination antimicrobial therapy
	IT to provide decision support and enhanced surveillance
	Antibiograms at patient and organizational level

Figure 9 Implementation framework of an antibiotic stewardship program (adapted from: BSAC. Antimicrobial Stewardship: From Principles to Practice – eBook 2018)[4]

2.2.2 Multidisciplinary ABS team

Although it is vital that the ABS program is rolled out hospital-wide, there needs to be a core team that is responsible and accountable for the program management and outcome. The composition of this team will depend on the resources available in an individual hospital as not every role will be available in all hospitals. Ideally, the team should comprise at least one infectious disease physician, a clinical microbiologist, and a clinical pharmacist (Figure 10).

Team members should have clearly defined roles and responsibilities and receive adequate training and resources to allow them to fulfil their duties. **The multidisciplinary team is responsible for the development of local guidelines, implementation of core interventions, and education of all hospital staff.**

On a day-to-day basis, the ABS team will:[4]

- **Consult** on individual patient management at the request of clinicians
- **Review prescriptions** for antimicrobial therapy
- **Advice on the optimization** of antimicrobial therapy
- **Promote conversion** from intravenous (IV) medication to oral (PO) options
- **Educate** through formal teaching sessions or ad hoc education on ward rounds

Core team	Optional members
• Infectious disease physician	• Nurses
• Clinical microbiologist	• Epidemiologist
• Clinical pharmacist	• Infection control specialist
	• IT resources

Figure 10 Members of an ABS team (adapted from BSAC. Antimicrobial Stewardship: From Principles to Practice – eBook 2018)[4]

2.2.3 Local guideline development

The development of local treatment guidelines is a good way for the ABS program to engage prescriber stakeholders and encourage them to develop consensus on antibiotic use. Local guidelines provide instructions on the application and minimum duration of antibiotic therapy, and should:

- **Provide clear recommendations for optimal antibiotic use** that are hospital-specific and based on national guidelines
- **Reflect hospital treatment preferences** based on local susceptibility, formulary options, and patient population
- **Optimize antibiotic selection and duration for common indications** like CAP, UTI, IAI, skin and soft-tissue infection and surgical prophylaxis
- **Include diagnostic approaches (if possible)** such as when to send diagnostic samples and what tests to perform, including indications for rapid-diagnostics and non-microbiologic tests (e.g. imaging, procalcitonin)

Figure 11 Local guidelines (adapted from: CDC. Core Elements of Hospital Antibiotic Stewardship Programs 2019)[2]

CAP Community-acquired pneumonia **UTI** Urinary tract infection **IAI** Intra-abdominal infection

2.2.4 Education

As part of a successful ABS program, the general public, patients, as well as healthcare staff should be educated on antibiotic resistance, potential adverse reactions from antibiotics, and optimal prescribing. In addition, all healthcare staff should be educated to demonstrate competency in the following:

- **Infection prevention and control**
- **Antimicrobial resistance and antimicrobials**
- **Prescribing of antimicrobials and antibiotic stewardship**
- **Monitoring and learning: continued professional development in antibiotic prescribing and stewardship**

Figure 12 ABS program education for healthcare staff (adapted from Public Health England, Antimicrobial prescribing and stewardship competencies, Online October 2013)[18]

2.2.5 Preauthorization and restriction or prospective audit and feedback

The two most effective ABS strategies are preauthorization of restricted antimicrobial agents and prospective audit and feedback (Figures 13 and 14). It is recommended that organizations choose to implement either one or a combination of both strategies depending on the hospital setting.

The primary advantage of prospective audit and feedback is that doctors do not lose prescribing autonomy due to the voluntary nature of the strategy, however, it can be very labor-intensive and expensive. An example of the prospective audit and feedback algorithm is shown in Figure 15.

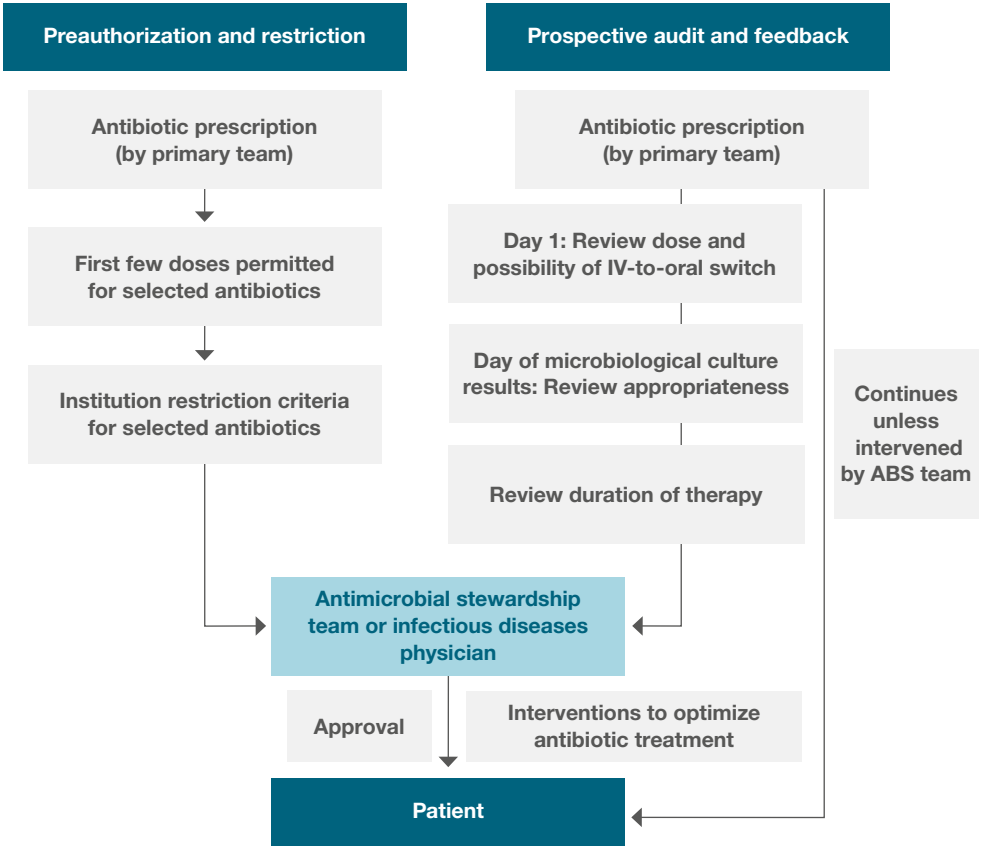


Figure 13 The two most effective antibiotic stewardship strategies: preauthorization and restriction vs. prospective audit and feedback (adapted from Chung GW et al., Virulence 2013)[19]

List of interventions considered as part of antimicrobial stewardship

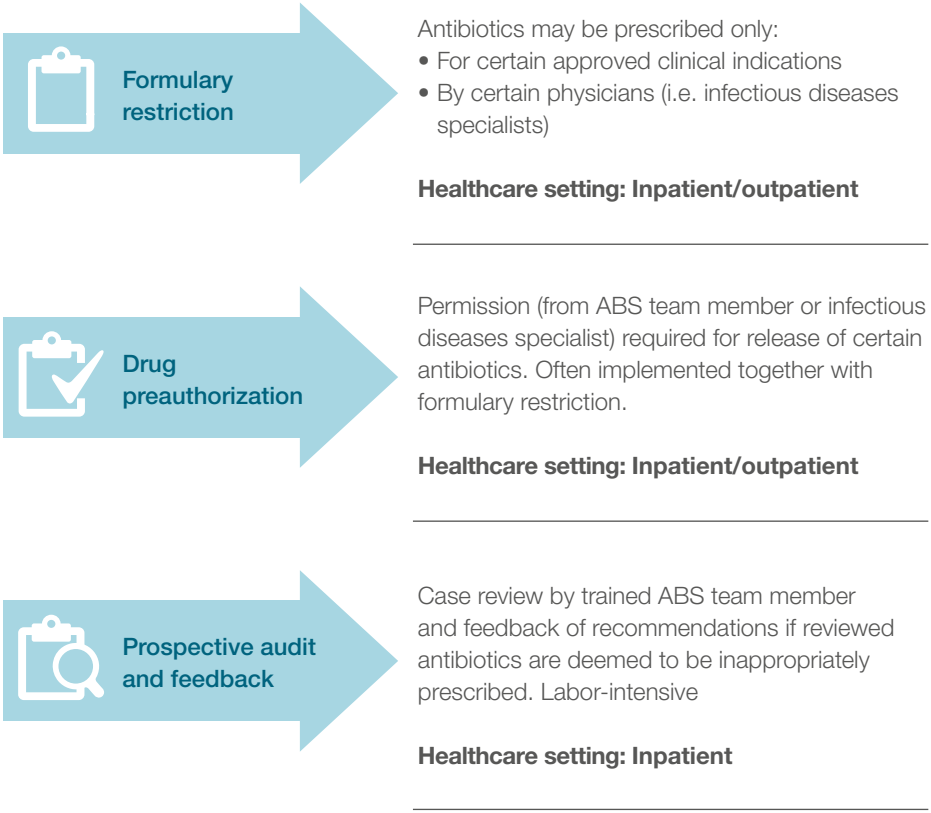


Figure 14 Description of interventions considered as part of antimicrobial stewardship (adapted from Chung GW et al., Virulence 2013)[19]

Audit-intervention-concurrent feedback

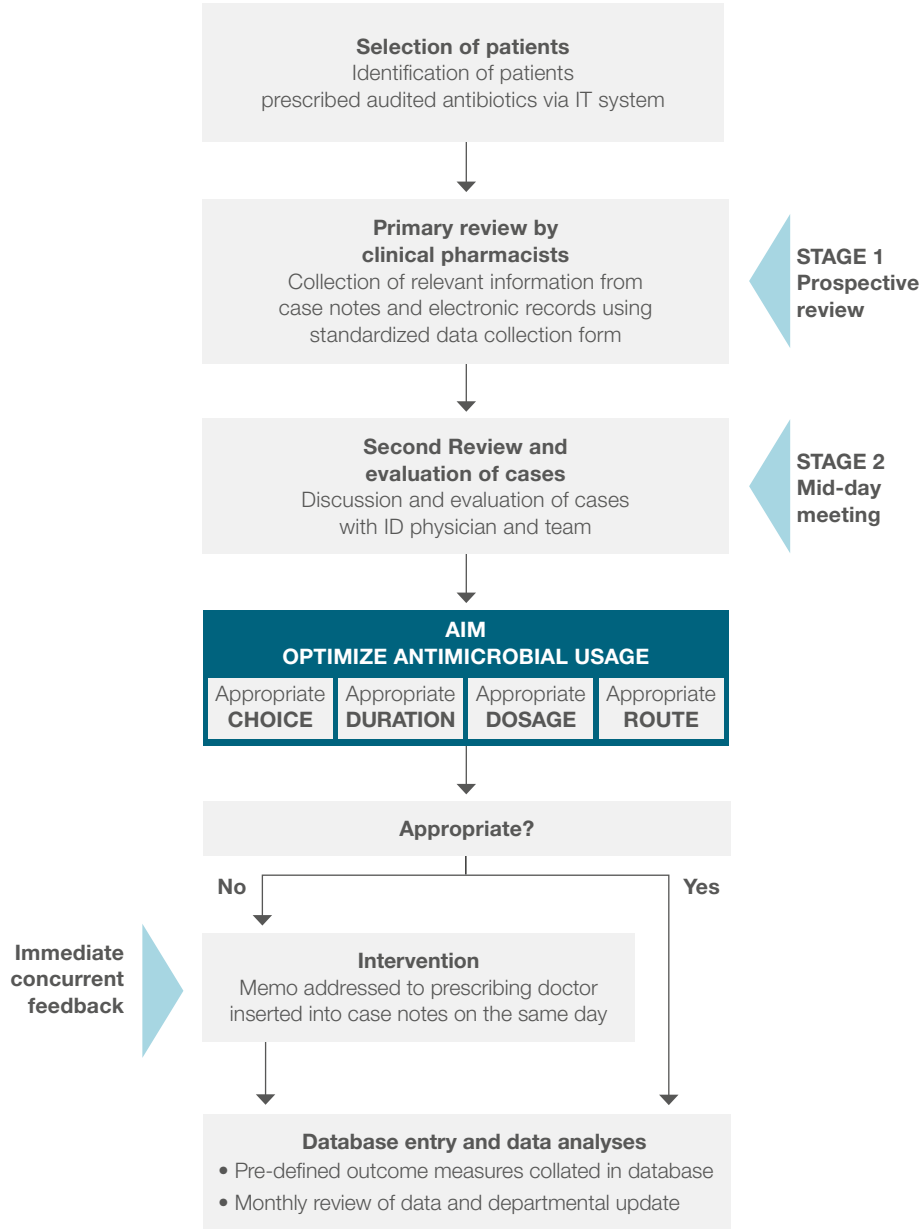


Figure 15 An example of a prospective audit and feedback algorithm (adapted from Loo LW et al., International Journal of Antimicrobial Agents 2019)[20]

2.3 Key measures of improvement

It is important to assess the impact of the stewardship intervention on clinical practice and outcomes. The ABS team must set clearly defined aims and objectives for their chosen areas of improvement and establish a clear plan of action how these goals will be achieved. Only by measuring the improvement indicators will the ABS team know whether the implemented measures have been effective.

- **Antibiotic use measures:** monitor and benchmark antibiotic use through standardized output, e.g. days of therapy (DOT), standardized antimicrobial administration ratio (SAAR) or defined daily doses (DDD)
- **Outcome measures** like *C. difficile* infections, antibiotic resistance or financial impact
- **Process measures** like tracking type and acceptance of recommended interventions, monitoring adherence to facility specific guidelines or the intravenous (IV) to oral (PO) ratio (IV/PO ratio)

Figure 16 Tracking key measures of improvement (adapted from: CDC. Core Elements of Hospital Antibiotic Stewardship Programs 2019)[2]

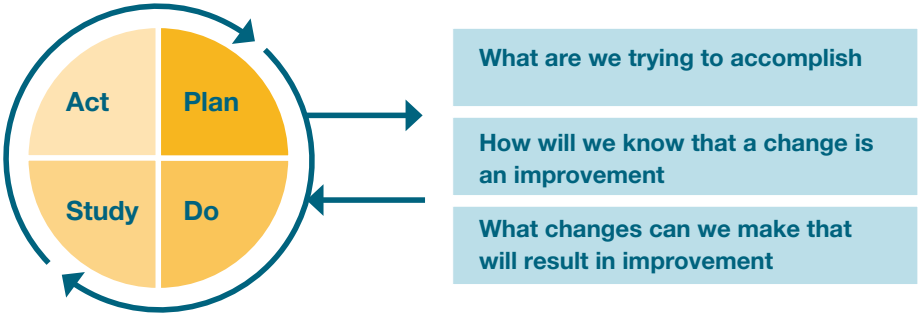


Figure 17 Using the Plan, Do, Study, Act framework for effective implementation (adapted from https://improvement.nhs.uk/documents/2142/plan-do-study-act.pdf)[21]

2.4 Key messages

An ABS program can be successfully implemented in any hospital as long as there is a **determined multidisciplinary core team** available that is empowered by the hospital leadership, with dedicated human, financial and IT resources.

Core tasks of the multidisciplinary team include the development of local guidelines, implementation of an antimicrobial prescribing method, e.g. preauthorization of restricted antimicrobial agents and/or prospective audit and feedback, and education of all hospital staff.

The impact of the ABS interventions on clinical practice should demonstrate benefits for patients (Figure 18).

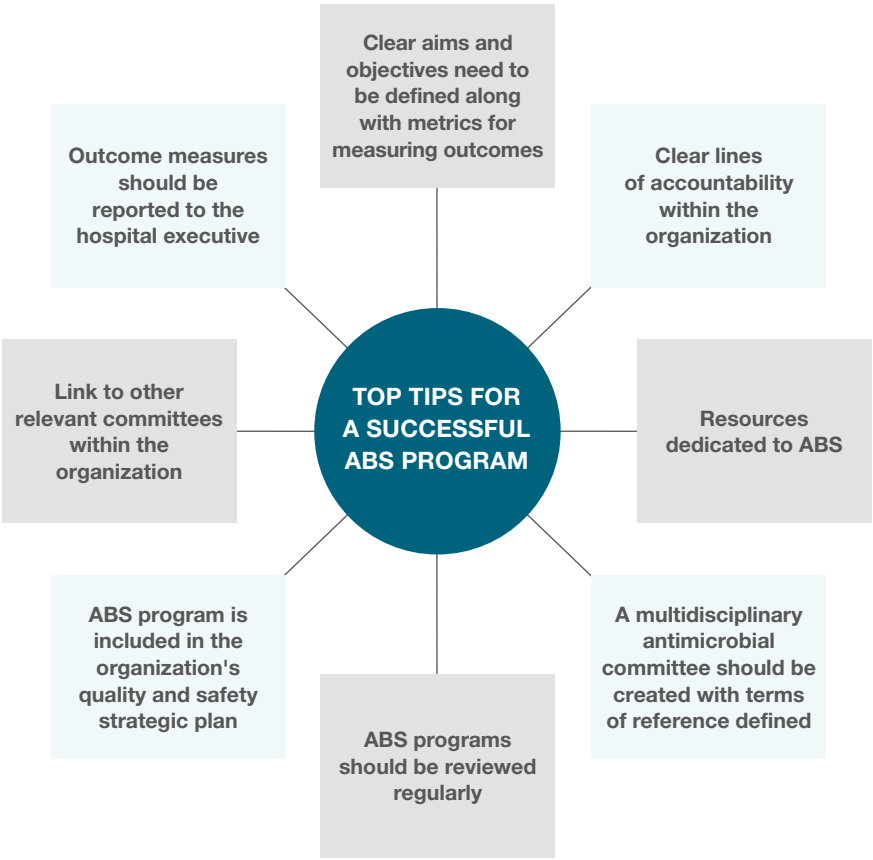


Figure 18 Top tips for a successful ABS program (adapted from: BSAC. Antibiotic stewardship from principles to practice – eBook 2018)[4]

PCT

Part 3 – Integration and impact of the biomarker procalcitonin as part of the antibiotic stewardship program

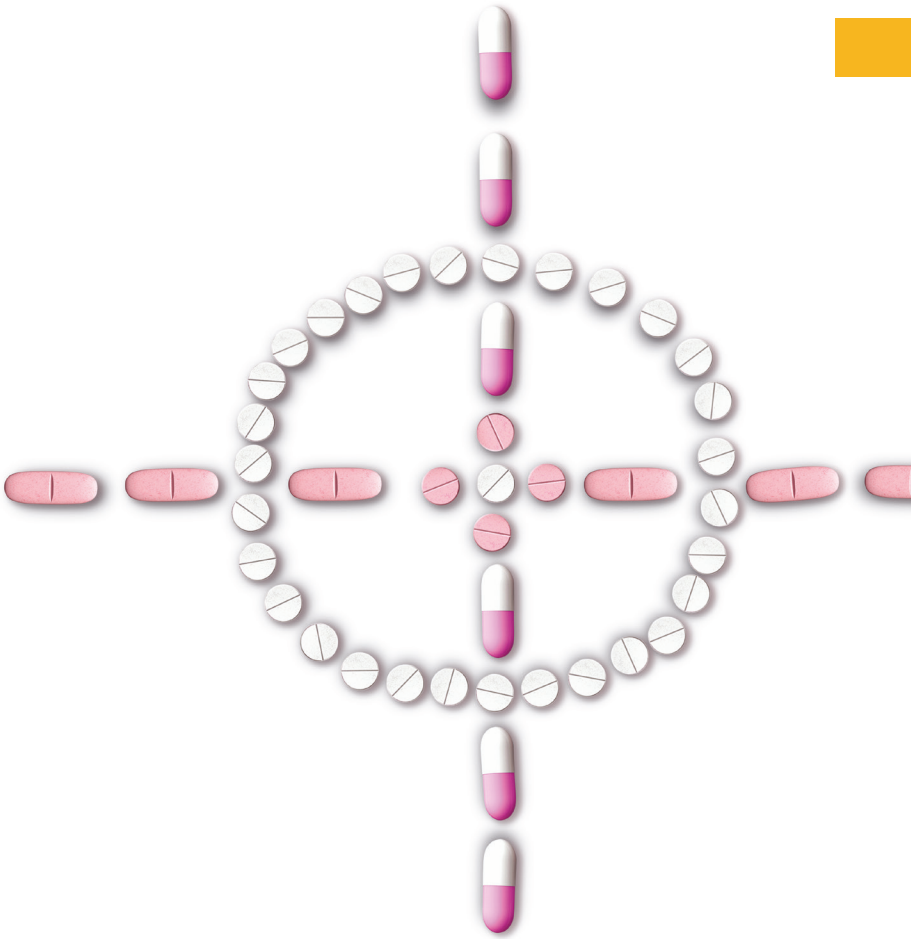
3.1 Diagnostics are an integral part of an ABS program

Diagnostics are an integral and essential part of an ABS program. Blood cultures and molecular diagnostics provide information if and which kind of pathogen is present, which can guide appropriate antibiotic prescription. In addition, blood biomarkers can give information on how the host is responding to the infection.

"Essential diagnostics: diagnostics that satisfy the priority healthcare needs of the population and are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and accuracy and comparative cost-effectiveness."[22]

Procalcitonin (PCT) is a rapid-reacting biomarker which indicates the host-response specifically to a bacterial infection. PCT provides information about the likelihood of a clinically relevant bacterial infection and the risk of progression to sepsis and septic shock and aids in antibiotic therapy decisions. The WHO, in their model list of essential in vitro diagnostics (EDL3), recognized the role of PCT for tertiary care facilities and above "to guide antibiotic therapy or its discontinuation in sepsis and lower respiratory tract infection."[6] **PCT is the only biomarker in the EDL that is recognized as an aid in antibiotic therapy decisions.**

Randomized controlled interventional studies have shown that integrating PCT into clinical decision making is beneficial for patients with respiratory tract infections and sepsis as it significantly reduced antibiotic exposure, infection-related adverse events, and mortality.[23,24,25]



Procalcitonin is now mentioned in the WHO model list of essential in vitro diagnostics as an aid for decisions on antibiotic therapy or its discontinuation.[6]

3.2 Consensus algorithm for B·R·A·H·M·S PCT use

Procalcitonin can be safely used for initiation of antibiotic therapy and for monitoring antibiotic treatment efficacy, together with the information given by the medical history, physical examination, and microbiological evaluation. An algorithm using B·R·A·H·M·S PCT for the safe and effective reduction of antibiotic use has been developed for both critically ill and non-critically ill patients, based on the clinical evidence and practical experience (Figure 19).[26]

Caution should be taken in patients with immune-suppression (including HIV), cystic fibrosis, pancreatitis, trauma, pregnancy, and high volume transfusion. B·R·A·H·M·S PCT-aided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis). For *S. aureus* bacteremia and candidemia infection, therapy duration should not be shortened below the minimal duration according to the respective guidelines. Instruction for the use of the in-vitro diagnostic tests should be consulted for correct intended use and interpretation of the results in specific indications.

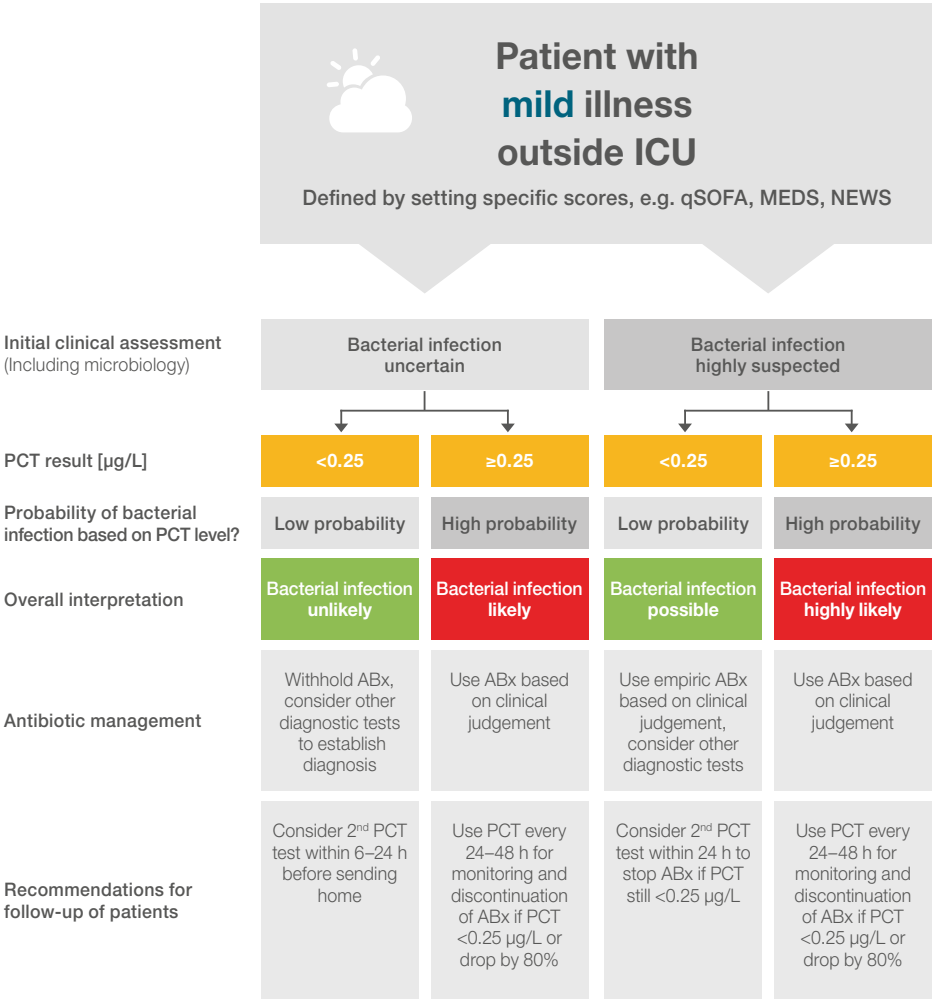


Figure 19a B·R·A·H·M·S PCT algorithm for antibiotics initiation and discontinuation in patients with mild illness outside of the ICU (adapted from Schuetz P et al., Clin Chem Lab Med 2019)[26]

ABx Antibiotics

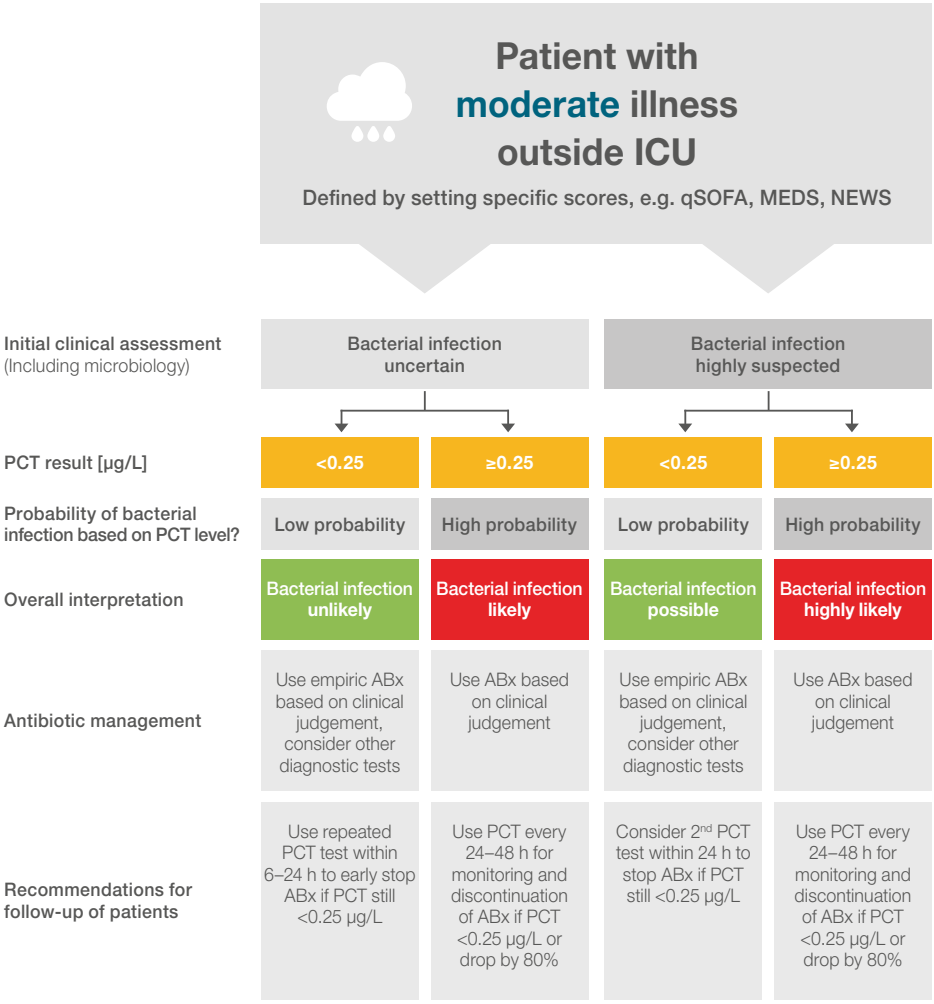


Figure 19b B·R·A·H·M·S PCT algorithm for antibiotics initiation and discontinuation in patients with moderate illness outside the ICU (adapted from Schuetz P et al., Clin Chem Lab Med 2019)[26]

ABx Antibiotics

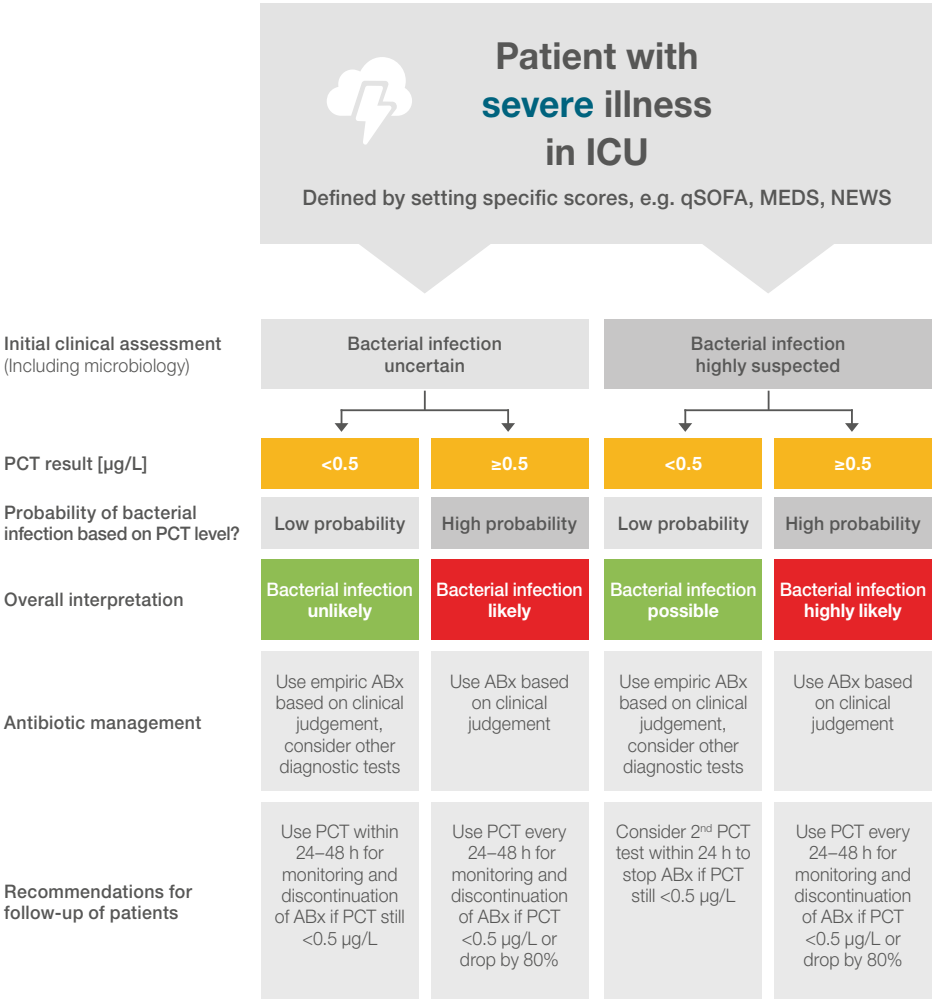


Figure 19c B·R·A·H·M·S PCT algorithm for antibiotics initiation and discontinuation in patients with severe illness in the ICU (adapted from Schuetz P et al., Clin Chem Lab Med 2019)[26]

ABx Antibiotics

3.3 Example of successful implementation of PCT within an ABS program in the USA

A single-center, pre-post, retrospective cohort study was conducted at the Five Rivers Medical Center, a community hospital in Arkansas, to evaluate the impact of adding PCT to existing ABS practices.[27] Four years of data were collected before and after PCT implementation and were compared in critical and acute care patients of all ages. After implementation, a baseline PCT was obtained on admission in patients with suspected bacterial infection and serial PCT measurement were repeated daily to evaluate effectiveness of therapy.

"The goal is to provide leading thought processes in patient management and use technology to enhance clinicians' ability to have the best options in their patients' clinical status, decision support, and improve outcomes through better clinical care."

Mike Broyles, PharmD
Pharmacy Director at the Five River Medical Center in Pocahontas, Arkansas (USA)

Dr. Broyles has more than 30 years of experience as a Hospital Pharmacy and Laboratory Director providing patients with current concepts in the clinical use of drugs with a focus on antimicrobial stewardship.

He has consulted for more than 25 of the 40 largest Integrated Healthcare Networks in the U.S. He has served on advisory boards and regularly speaks to industry, serving hospitals ranging from 35 to 1200 beds in size. Most recently, he served as a global expert consensus member on PCT-aided antibiotic therapy in hospitals and presented to the FDA in the most recent claim approval for use of PCT in sepsis and LRTI.

The addition of PCT to the existing antimicrobial stewardship practices at Five Rivers Medical Center contributed to significant reductions in median days on antibiotic therapy, all-cause readmission, adverse events from antimicrobials, all-cause hospital mortality and *C. difficile* infections (Figure 20).

In addition, implementation of the PCT protocol significantly reduced the costs per patient with sepsis and lower respiratory tract infections (LRTI) (Figure 21).

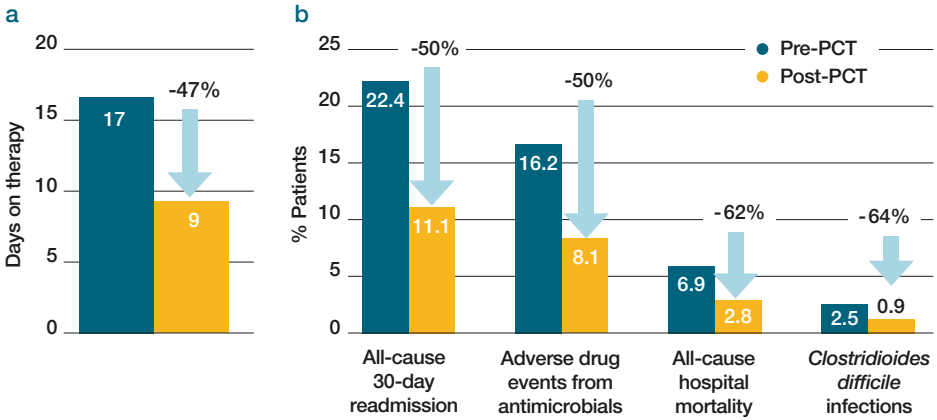


Figure 20 (a) Median days on therapy four years before PCT implementation (pre-PCT, 985 patients) and four years after PCT implementation (post-PCT, 1167 patients). (b) Percentage of patients suffering complications pre-PCT and post-PCT (adapted from Broyles MR et al., Open Forum Infect Dis 2017)[27]

	Pre-PCT	Post-PCT	Difference post-pre
Cost per sepsis patient	$52,055	$26,433	$-25,611
Cost per LRTI patient	$15,738	$12,109	$-3,629

Figure 21 Hospital costs per patient in the four years preceding PCT implementation (pre-PCT) and four years after PCT implementation (post-PCT) (adapted from Voermans AM et al., OMICS 2019)[28]
A negative value for the difference indicates cost savings in the post peaked phase.

To get the most out of the PCT-aided algorithm, the following need to be considered in order to integrate PCT into the hospital workflow:

- There should be clear protocols to start, revise and stop antibiotic therapy, approved by medical staff and pharmacy
- The PCT protocol should be placed in the top admission diagnoses that required or may require the use of antibiotics
- For suspected infections, PCT should be a pre-checked box on the admission order sets and listed as a priority item
- PCT-aided ABS starts with the admission order sets for the emergency department (where the majority of admissions enter) and continues with all hospital admissions using the electronic medical record system order sets
- The pharmacy reviews all antibiotic use or potential diagnoses for appropriate antibiotic use
- The PCT protocol can be ordered and followed by the pharmacist if omitted or unchecked by clinician or for a less common diagnosis that was not in order sets

Figure 22 Considerations before the integration of PCT in an ABS program (adapted from Broyles MR et al., Open Forum Infect Dis 2017)[27]

3.4 Example of successful implementation of PCT within an ABS program in Singapore

Singapore General Hospital has been running a multidisciplinary ABS program since 2006. The success of this program has mainly been due to the support received from the senior hospital administration, the government, and the clinical teams of the participating departments. Successfully implementing the ABS program was based on involving stakeholders from the top-down and bottom-up together. Giving timely prospective feedback and engaging regularly and frequently with clinical departments on further improvements has been very important for adoption. PCT was introduced in 2008 as part of the ABS program. It is used as an aid, in conjunction with clinical judgement, as an objective marker for the decisions on the safe discontinuation of antibiotics.

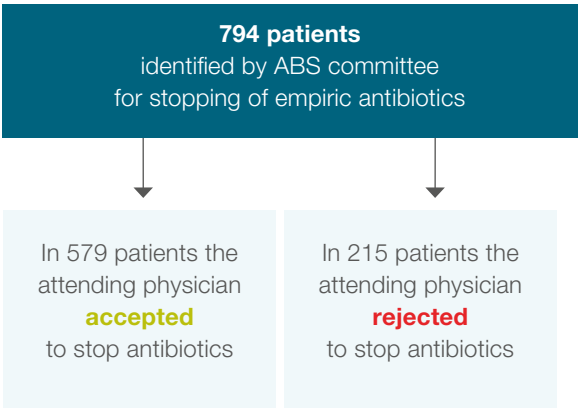
Andrea Kwa, PharmD
Pharmacy Clinician Scientist with the Singapore General Hospital, and an Associate Professor with the Duke-National University of Singapore, Emerging Infectious Diseases Program, Singapore.

Dr. Kwa specializes in critical care medicine and infectious diseases. She has a huge passion for research involving antimicrobial resistance (in-vitro and in-vivo) and health services research on antimicrobial stewardship. To-date, she has authored more than 90 peer-reviewed publications and delivered more than 150 presentations.

As an avid reviewer, she has contributed to many scientific journals including Clinical Infectious Disease and Clinical Microbiology & Infections.

"The success of any ABS program is that it must ultimately have a continuous positive impact on patient care in terms of safety."

The impact of implementing PCT into the ABS program was significant. As shown in Figure 23 below, when physicians accepted the ABS program recommendations aided by PCT and clinical judgement, it led to a significant reduction in antibiotic exposure and a shorter length of stay, without negatively impacting patient outcomes measured by 14-day all-cause mortality and 14-day readmission due to infection.[20] The algorithm used for the audit concurrent feedback from Singapore General Hospital is shown in Figure 15.



Mean PCT* (µg/L)	**0.18**	**0.16**	n.s.
ABx duration (days)	**2.72**	**5.33**	-2.61**
LOS (days)	**7.98**	**15.39**	-7.41**

Figure 23 Outcome analysis for patients where the ABS committee recommended discontinuation of empiric antibiotics within 24 h of prescribing based on a ABS protocol including PCT (adapted from Loo LW et al., International Journal of Antimicrobial Agents 2019)[20]

* PCT was available for >70% of patients
** $p<0.01$ accepted vs rejected intervention

ABS Antibiotic stewardship **ABx** Antibiotic **LOS** Length of stay **NS** Not significant

3.5 Example of successful implementation of PCT within an ABS program in Greece

Long-term use of antibiotics can increase the risk of infections caused by *Clostridioides difficile* (CDI) and multidrug-resistant organisms (MDRO) in critically-ill patients, which can lead to poor clinical outcomes.

The PROGRESS[25] study, a multi-center, real-world pragmatic trial in Greece, showed that using PCT as an aid for the decision for early discontinuation of antibiotic therapy in sepsis patients reduced the duration of antibiotic treatment compared to standard of care. The incidence of infection-associated adverse events like infections by CDI, MDRO or associated deaths was reduced in the PCT-group, while 28-day survival was significantly improved. This indicates that PCT-aided decision-making in sepsis is safe and provides long-term benefits with a potentially substantial public health impact.

The benefits of PCT-aided decision-making "may have substantial impact on public health, particularly for countries with high antimicrobial consumption."[25]

Evangelos J. Giamarellos-Bourboulis, MD, PhD
Professor of Internal Medicine at the National and Kapodistrian University of Athens, Medical School; Supervisor of Immunology of Infectious Diseases Section at ATTIKON University Hospital

Prof. Giamarellos-Bourboulis' research interests include the pathogenesis of sepsis with emphasis on immunoparalysis, innate immunity, and in-vitro activities as well as pharmacokinetics of antimicrobials and their interactions on multidrug resistance species.

He is a guest professor at the Center for Sepsis Control and Care of the Jena University Hospital in Germany and president of the European Shock Society and chairman of the European Sepsis Alliance. He has published 400 peer-reviewed articles with more than 17,000 citations.

The use of the PCT algorithm in the study protocol (Figure 24) led to an approximate 50% shorter median duration of antibiotic therapy independent of the cause of the infection (Figure 25).

This led to a reduction of infection-associated adverse events (15.3% vs 7.2%, *p*:0.045) and in-hospital and 28-day mortality (28.2% vs. 15.2%, *p*:0.02), both by almost 50%. For the PCT-aided arm, the odds ratio for infection-associated adverse events was shown to be independent from fecal colonization, but not so in the standard of care arm. This indicated that although there was some initial colonization, after exposure to antimicrobials in the PCT-aided arm, early discontinuation did not allow development of clinical infection. The increased incidence of infections by MDRO and *Clostridioides difficile* in the standard-of-care arm could be explained by the effect of long-term antibiotic exposure on the gut microbiota.

Study design

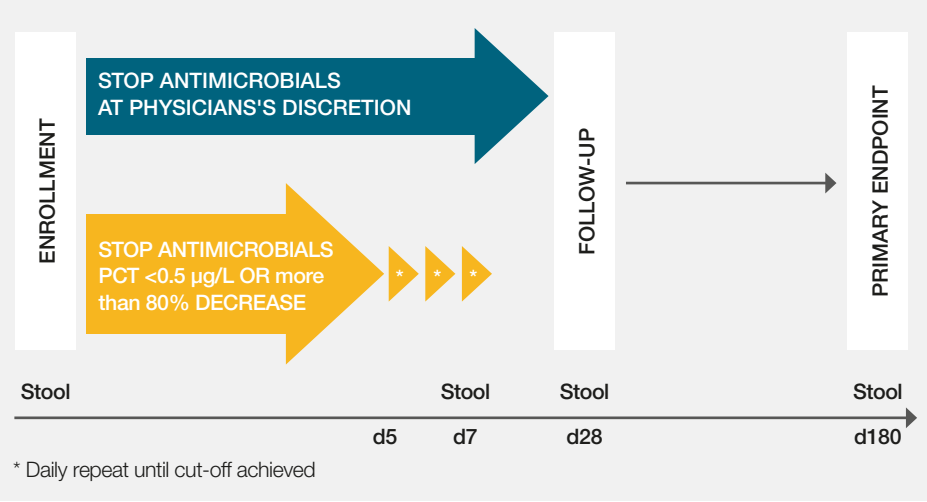


Figure 24 Study design of the PROGRESS trial (adapted from Kyriazopoulou E et al., Am J Respir Crit Care Med 2020)[25]

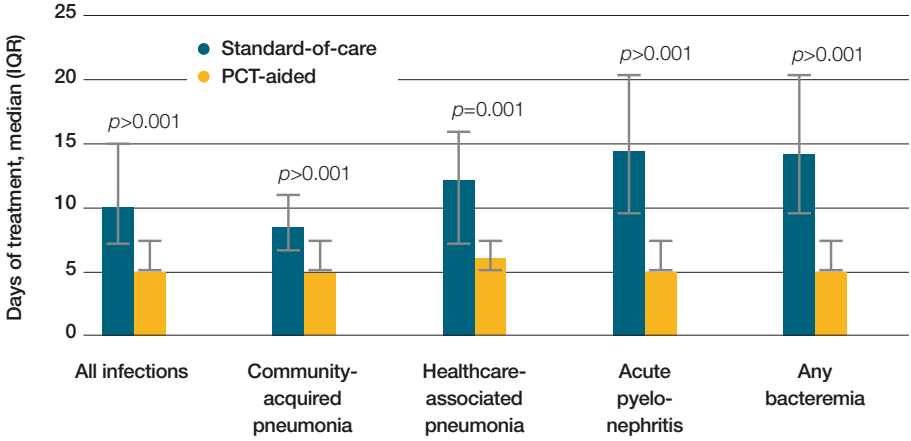


Figure 25 Median length of antibiotic therapy in 266 patients (adapted from Kyriazopoulou E et al., Am J Respir Crit Care Med 2020)[25]

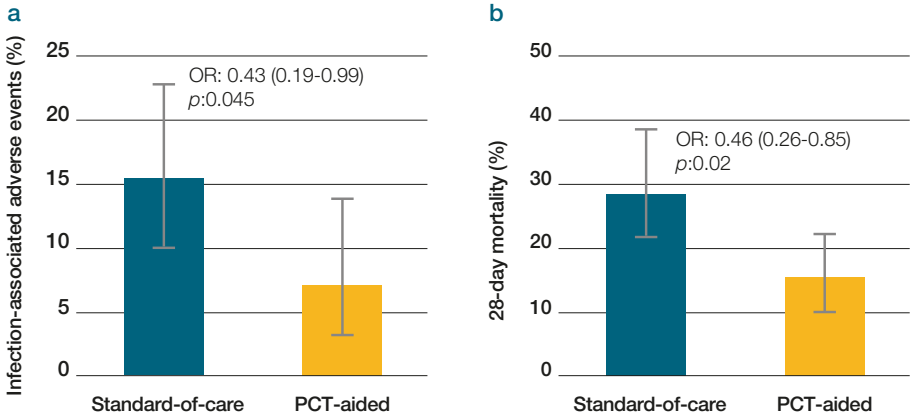
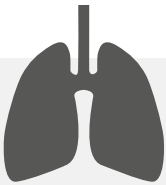


Figure 26: (a) primary endpoint of the study, infection-associated adverse events at six months (composite endpoint consisting of incidence of new CDI, incidence of new MDRO infection and infection-associated death by baseline CDI or MDRO), and (b) secondary endpoint, 28-day mortality (adapted from Kyriazopoulou E et al., Am J Respir Crit Care Med 2020)[25]

IQR Interquartile range **OR** Odds ratio **CDI** *Clostridioides difficile* infection
MDRO Multi drug resistant organism

3.6 Further evidence in selected indications



Lower respiratory tract infections (LRTI)

Schuetz P et al., Lancet Infect Dis 2018 [29]

- PCT-aided decision-making has been shown to significantly reduce antibiotic exposure in patients with LRTI through reduced antibiotic prescription in low-risk settings and low-risk patients, and by shorter duration and earlier discontinuation of antibiotics in high-risk patients
- PCT-aided antibiotic treatment resulted in significantly lower antibiotic side-effects and mortality

Surgical intensive care unit

Hohn A et al., Infection 2015 [30]

- PCT-aided ABS program resulted in a 21.2% decrease in antibiotic use density (daily doses/1,000 patient days) with no increase in mortality
- Led to a marked reduction in the consumption of aminoglycosides, cephalosporines, and quinolones

Neonates

Stocker M et al. and the NeoPInS Study Group, Lancet 2017 [31]

Standardized risk assessment with PCT is shown to be superior to the standard of care:

- Reduced duration of antibiotic therapy and shortened hospital stay
- Resulted in a low rate of re-infections and no study-related mortality

Intensive care unit

de Jong E et al., The Lancet Infectious Diseases 2016 [9]

- PCT-aided antibiotic therapy significantly reduced treatment duration by 2 days and antibiotic consumption by 19% when compared to standard of care in a setting that already had comparatively short antibiotic therapy regimes
- PCT-aided antibiotic therapy among critically-ill patients was associated with a significant reduction in mortality at 28 days and 1 year when compared to standard of care

3.7 Key messages

Diagnostics are an integral part of an ABS program. In addition to blood cultures and molecular diagnostics, the host-response biomarker PCT can aid in the clinical management of patients.

PCT can be safely used to monitor antibiotic treatment efficacy, together with the information given by the medical history, physical examination, and microbiological evaluation.

Evidence from multicenter studies and meta-analyses have shown the PCT algorithm to be safe and effective in reducing antibiotic prescriptions and reducing adverse events in adults, children, and neonates across multiple settings globally.

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