Rational empiric antibiotic therapy in clinical practice and policy making: uncertainties, probabilities, and ethics

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General discussion and summary

Antimicrobial resistance (AMR) represents a serious clinical and public health challenge. The emergence of drug resistant bacteria has been paralleled by a stagnation in the antibiotic development pipeline. Currently, the biggest threat is posed by the antimicrobial resistant ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacter species) pathogens.[1] These pathogens are characterized by potent drug resistance mechanisms and are a leading cause of severe multidrug resistant infections, especially in the nosocomial setting. The acquisition of antimicrobial resistance genes by ESKAPE pathogens and other multidrug resistant organisms (MDRO) has reduced the treatment options for serious infections, and increased the death rates due to treatment failure worldwide.[2]

Infections with pathogens with reduced susceptibility to antibiotics are associated with higher mortality compared to infections with their more susceptible counterparts.[3] Data suggest that this disparity may -in part- be the result of a mismatch of empiric therapy.[3,4] Therefore, the changing epidemiology of AMR requires constant adaptation of antimicrobial policy guidelines. Increasing resistance in major human pathogens, demands further broadening of the empiric therapy with the aim to ensure adequate coverage. At the same time, this leads to more consumption of broad-spectrum antibiotics and contributes dramatically to the rising prevalence of resistance. Strategies to target the use of antibiotics in the empiric setting are needed to escape from this vicious cycle of increasing antimicrobial consumption and development of resistance in human pathogens.

No matter the strategy, empiric antibiotic therapy is inevitably accompanied by a certain degree of uncertainty, as is ubiquitous in medicine.[5] Uncertainty about the pathogen and the antimicrobial susceptibility pattern, are among the primary concerns. However, uncertainty is not limited to the microbiological aspect alone. This thesis addressed the uncertainties that are associated with empiric antibiotic therapy, how they affect daily decision making, and how they can be tackled in antibiotic policy making and antibiotic stewardship. In this chapter the results of these studies are summarized, and the potential implications are discussed.

FROM UNCERTAINTY TO PROBABILITY

Time to positivity as a tool in empiric antimicrobial treatment

At the time of the first assessment of the patient, the clinical diagnosis often remains uncertain. Blood cultures are essential in the diagnostic process, in particular when the source of the infection is not yet evident and the presence of bacterial infection is questionable.[6] Historically, diagnosing or excluding bloodstream infection is the weakest link in the diagnostic process, as bacterial growth of blood samples in culture media takes several days. Because of the modernisation of blood culture methods, and the development of continuous monitoring systems, the time to positivity (TTP) of blood cultures has been reduced substantially during the past decades. In **Chapter 2** we describe the potential of time to positivity (TTP) in the diagnostic approach of patients with suspected bacterial infections. The study shows that, in patients with bacteraemia, the majority of blood cultures reached positivity within 24 hours. The probability of blood culture positivity after 24 hours was 1.8% (95% CI 1.46-2.14%). The knowledge that the probability of bacteraemia is very low when blood cultures have remained negative for 24 hours is valuable for clinical decision making. In particular if further diagnostics aimed at identifying bacterial infection have not revealed an infectious source, the antibiotic therapy deserves to be re-assessed.

For the application of this probability to the bedside, the pre-test probability of bloodstream infection (BSI) in the individual patient should be considered. The pre-test probability is largely dependent on the clinical syndrome, for example septic versus non-septic patients, but may be difficult to estimate. Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection. However, the majority of patients in whom blood cultures are obtained, does not fulfill the sepsis criteria and have a relatively lower pre-test probability of BSI. When the pre-test probability is high, for example in septic shock, the probability of bacteraemia at T=24 may rise accordingly. On the other hand, in patients with sepsis and septic shock, bacterial load is likely to be relatively high, and therefore TTP may actually be shorter.[7] So, when it comes to the probability of BSI at T=24 hrs., the shorter TTP may – at least to some extend- counteract the relatively high prevalence of BSI in septic patients.

A second factor to consider with regard to TTP, is the patient population. TTP may differ between patient populations with BSI, either because of patient characteristics or because of the specific distribution of pathogens.[8] Patients with neutropenia constitute a highly relevant subpopulation. During neutropenia, i.e an absolute neutrophil count below 0.5 x 10^9 cells/L, patients are more susceptible to bacterial bloodstream infections, which are associated with substantial morbidity and mortality.[9] However, it is notoriously difficult to distinguish bacterial infection from viral of fungal infection or non-infectious pathology in this patient population.[10] **Chapter 3** shows that the finding in the general population – that the probability of BSI is low after 24 hours – also applies to patients with neutropenia. For some of the major pathogens, such as *Staphylococcus aureus*, Enterobacterales and *Pseudomonas aeruginosa*, median TTP was low in patients with neutropenia as compared to the general patient population. This may be explained by the fact that in the (near) absence of neutrophils, the bacterial load is higher, reflected in a low TTP. In patients with neutropenia, excluding bacteraemia at an early time point is at least as important as in the general population, as the differential diagnosis of febrile neutropenia is broad. A low probability of BSI at T=24 hrs. may warrant early diagnostics, i.e. additional imaging looking for insidious fungal infections.

Although guidelines advise extensively on the initial choice of empiric antibiotics in sepsis, there is limited research on the safety of de-escalation of antibiotic therapy, in immunocompetent nor immunocompromised patients. Currently, in immunocompetent adults, the consensus is to discontinue antibiotic therapy when blood cultures remain negative for 48 hours up to 96 hours and no primary site of infection has been identified. With the results from Chapter 2 and 3, the 48 hour timespan should be questioned. The current broad spectrum empirical treatment of 48 hours may thus be unnecessarily longer than the time that is needed to diagnose bacteraemia. In the meanwhile patients are exposed to potentially toxic therapy, antimicrobial resistance is enhanced and health care costs increased. Both in the general patient population and in patients with neutropenia, the potential gain is significant. The benefit of a TTP-guided de-escalation approach would not be limited to the individual patient. Considering the vast number of patients that present each day with suspected bacterial infections, it would impact overall antimicrobial consumption as well.

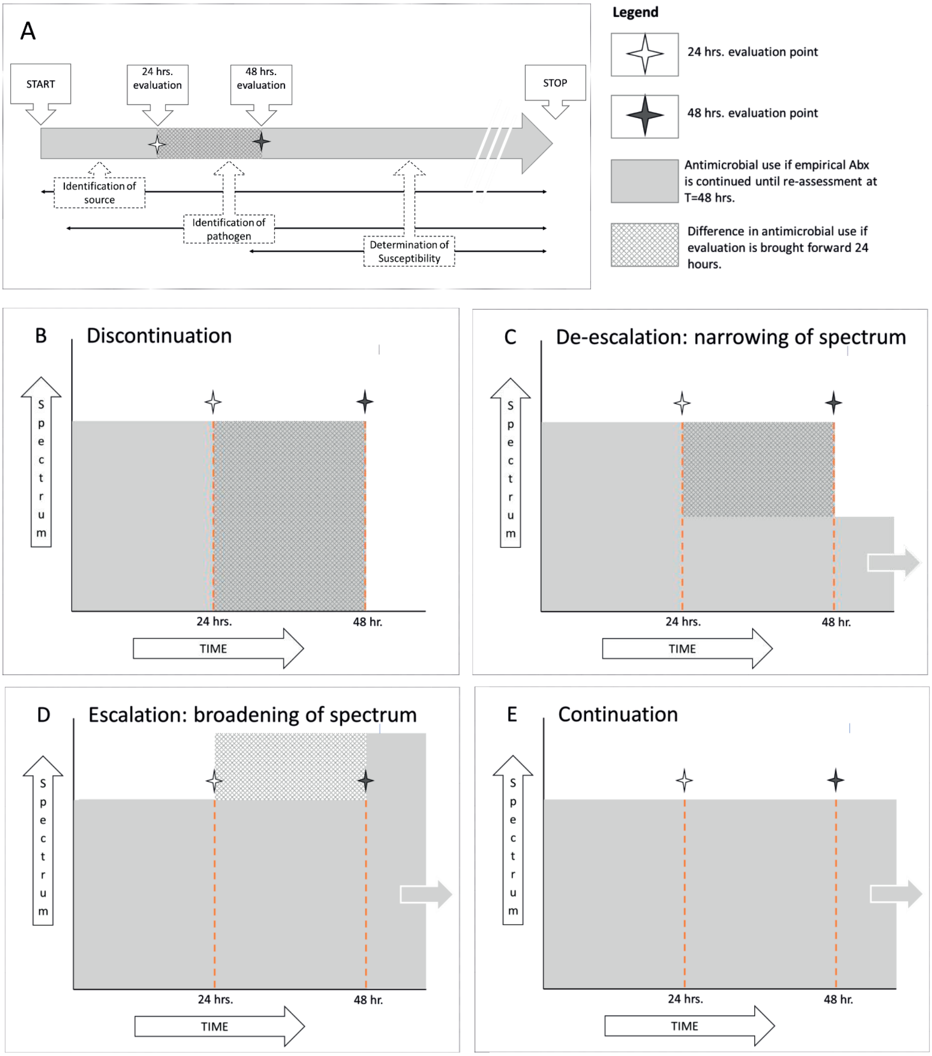
In addition to its value in the assessment of the probability of BSI, TTP may also be helpful in determining the probability of BSI with a specific class of pathogens. The distribution of pathogens is relevant, as this may guide early de-escalation strategies. For example, **Chapter 3** shows that in patients with febrile neutropenia, the probability of BSI with a Gram-negative aerobic pathogen is very unlikely when blood cultures have remained negative for 24 hours. These results were confirmed in a recent prospective study.[11] Guidelines for the treatment of febrile neutropenia recommend empirical treatment for a minimum of 48-96 hours. To address the relatively high prevalence of colonization with MDRO's in patients with onco-haematological disease, the recommended regimens are rather broad spectrum and include reserved antimicrobial agents. In the unlikely event of a BSI with a TTP of more than 24 hours, the pathogens are most often Gram-positive and/or anaerobic. Therefore, there is no rationale to delay the reassessment of the spectrum of Gram-negative antimicrobial treatment beyond 24 hours, because of pending blood culture results, as current international guidelines recommend to do.[12] So, in addition to the potential value for the duration of antimicrobial therapy in general, TTP may provide guidance with respect to the spectrum of empiric therapy, at different points in time.

Further research is needed to assess whether the duration of empirical antibiotic therapy and/or its spectrum can be safely reduced using TTP. Informing the physician about the remaining probability of blood culture positivity in his patient at T= 24 hours, could in itself be an intervention that affects diagnostic strategy and/or empirical therapy. Obviously, blood culture positivity is merely one of the factors that guide re-assessment of empirical therapy. Knowledge of a low probability cannot directly be translated to a potential for safe de-escalation. The clinical re-evaluation of the patient and the results obtained with other diagnostics, i.e. microbiological tests and imaging, are at least equally important. The outcome of re-assessment at 24 hours may therefore be continuation of antibiotic therapy or even escalation, despite the preliminary blood culture negativity. The different scenarios are depicted in figure 1. The real potential of TTP in decision making, is that it enables incorporating the factor time in the differential diagnosis of bloodstream infection. With TTP, antimicrobial therapy may be tailored to optimally fit the probability of BSI versus alternative (infectious or non-infectious) syndromes.

In **Chapter 4** TTP is used as part of a clinical rule in patients with *Staphylococcus aureus* bacteraemia (SAB). The purpose of this decision rule was not to diagnose BSI with *S. aureus*, but to differentiate between uncomplicated and complicated SAB. A risk score, composed of both clinical data and TTP was developed and validated externally. The risk score performed fairly well in predicting complicated SAB. The risk score is however insufficient to guide decision making ‘standing on its own’, but enables a more accurate assessment of the probability of complicated SAB. This chapter illustrates that TTP may not merely be used for the assessment of the probability of BSI over time, but also for risk assessment and prognosis in SAB specifically.

There are limitations to the use of TTP in clinical practice. TTP reflects the bacterial load in the blood and the microbial growth rate, but it is merely an indirect measure. As a result, the use of TTP in clinical practice is hampered by many confounding factors, most importantly variation in the volume of blood in the bottles and variation in transportation logistics. The time from collection of the blood culture sample to loading of the bottle differs between hospitals. This affects TTP, limiting the generalizability of the results, both in this thesis and in other publications. Future studies should be of a multicenter, prospective design and account for these aspects. It is nevertheless worth supporting further efforts to make use of the valuable information that TTP carries, that up till now remains hidden for clinicians.

Figure 1. Effect of early (24 hrs.) compared to late (48 hrs.) re-evaluation of empiric antimicrobial therapy on antimicrobial consumption in 4 different scenarios.



***Legend** A) The timeline of antimicrobial therapy*, in a patient with suspected bacterial infection. The source of infection and/or the causative pathogen, cannot always be identified and the timing is variable. Re-evaluation of empirical antimicrobial therapy at 24 hours, compared to 48 hours, has a potential impact on antimicrobial consumption of 24 hours and is largely dependent of the findings at reassessment. In all exemplary scenario's (B to E) the patient presents with sepsis of unknown origin and empiric treatment with a third generation cephalosporin is started. *B) Therapy is discontinued*. Example: the patient is stable at re-assessment, blood cultures are negative and there are no signs of localized infection. *C) Therapy is de-escalated* to a narrower spectrum. Example: blood cultures have remained negative at T=24 hours, and re-assessment reveals pneumonia. Therapy is narrowed to penicillin *D) Therapy is escalated* to a broader spectrum. Example: at the 24 hour re-assessment, the patients is hemodynamically unstable and deteriorating, empiric therapy is broadened by adding an aminoglycoside. *E) Continuation*. Example: At T=24 the patient is clinically stable. Blood cultures have remained negative. The most probable source is a urinary tract infection. Therapy is continued awaiting urine cultures.

Increasing antimicrobial resistance and the empiric treatment of sepsis and bacteraemia

Previous chapters of this thesis provide insight in the probability of bloodstream infection at different points in time. The next question is whether the causative pathogen is susceptible to the institutional antibiotic sepsis therapy. Empiric antibiotic treatment needs to be tailored to the local setting, accounting for the local epidemiology of pathogens. Worldwide the prevalence of pathogens with resistance to empiric sepsis therapy is increasing. When to change standard sepsis therapy to a broader spectrum, is a recurrent dilemma. Using local clinical and microbiological data, **Chapter 5** provides insight in the probability of a mismatch of empiric therapy if different antibiotic strategies were to be applied. The study shows that treatment adequacy rate can be increased, without increasing inappropriate reserve antimicrobial consumption, by tailoring antimicrobial therapy based on the probability of infection with a MDRO. We proposed a method to calculate the probability of adequate empiric therapy in a predefined population and to calculate the associated antimicrobial consumption. The number needed to treat (NNT) provides insight into the number of patients that need to be treated with a reserve antimicrobial agent to prevent an antibiotic mismatch in one patient. With the proposed method, different antibiotic strategies can be compared.

To draw conclusions from the estimated NNT of different antibiotic strategies, it is essential to consider the consequences of a mismatch in BSI. Although antibiotic therapy may be the cornerstone in the treatment of bacterial infections, the magnitude of the effect of a mismatch on patient survival is still a matter of debate. To decide on antibiotic therapy, and which adequacy rate of empiric therapy is – or is not- to be accepted, knowledge on the effect of a mismatch in patient outcome is essential.

Chapter 6 shows that, in a cohort of patients with BSI, a mismatch of empiric therapy was not independently associated with 14 day mortality. Disease severity scores were relatively low in the patient cohort, and therefore the results are not applicable to patients with severe sepsis and septic shock.[13] In these patients there are theoretical grounds and previous studies indicating that delays in instituting adequate antimicrobial therapy are indeed causally linked to mortality. Nevertheless, the data described in Chapter 6 suggest that, overall, the magnitude of the effect of adequate empiric therapy in BSI may be overestimated in daily clinical practice. Mortality in BSI is multifactorial and empiric antibiotic therapy may merely be a piece of the bigger puzzle. A correct diagnosis, adequate fluid resuscitation, adjustment of antibiotics based on culture results, and source control, may be even more important determinants of patient survival. The fact that adequate empiric therapy may not be the 'holy grail', is relevant when evaluating the NNT to prevent a mismatch of antibiotic therapy. Ultimately, we do not aim to treat the micro-organism, but the patient that has the infection.

FROM PROBABILITY TO DECISION MAKING

Decision making in clinical practice

As described in previous chapters, prescribing antimicrobial therapy -by its very nature- involves decision making under uncertainty.[14,15] Under such uncertainty, antimicrobial prescribing is not solely driven by an objective consideration of the available facts, as no human behaviour is. It is driven by attitudes and values, in response to intrinsic and extrinsic stimuli. For example social team dynamics and personal reputation, among others, may be prominent determinants of prescription behaviour. In **Chapter 7**, a theoretical framework was developed to describe the determinants of antibiotic prescription behaviour. Decision making under uncertainty is – and will always be- entangled with medical practice. Therefore medical students should be educated on the determinants of their own professional behaviour to raise awareness of the complexity of the decisional environment.[16] Education on the non-medical factors, such as social team dynamics, that may influence the decisions doctors make in daily practice, is underrepresented in medical curricula.[14]

Teaching the clinical examples of cognitive biases in decision making creates awareness and may increase the resistance of medical students to these effects. An illustration is the propensity to resolve uncertainty by action rather than inaction and how this is likely to result in overly broad antibiotic therapy. A successful balance of certainty and uncertainty can only be achieved if professionals are aware of just how complex the decisional environment is and what the pitfalls are.

Education on determinants of decision making in medicine should not stop with attaining the medical degree. Some of the strongest determinants of prescription behaviour, such as hierarchy and team dynamics, become even more apparent on the working floor. Discussions in peer group meetings may raise alertness to social aspects that influence medical decision making, and provide doctors with experience and tools to recognize and counteract potentially undesirable factors.

On a different level, knowledge of the determinants of antibiotic prescribing may be used for stewardship purposes.[17] For example, in order to efficiently improve adherence to antibiotic guidelines, it is essential to identify the determinants of non-compliance and target the improvement strategies accordingly. Further research should therefore focus on quantifying the relative importance of individual determinants of antibiotic prescribing.[18]

Antibiotic policy making

The first part of this thesis addresses uncertainties associated with empiric therapy and provides a starting point to estimate the probability of BSI and antimicrobial resistance. It enables the adjustment of empiric antimicrobial therapy to the local pathogen prevalence and susceptibilities, as current guidelines on antibiotic stewardship stress to do.[19] However, even the most advanced calculations, will not solve the central question: when to escalate empiric therapy to a broader spectrum. Ultimately it needs to be decided which adequacy rate and which NNT are acceptable. This is a question that may only be answered when both clinical data, local epidemiology and ethics are combined in a balanced way. A method to determine the antimicrobial resistance threshold above which antibiotic therapy should be adjusted to a broader spectrum, has never been universally agreed upon.

In **Chapter 8** we have constructed a framework to combine clinical and epidemiological data with ethics, to address antibiotic policy dilemma's. The first part of the framework is aimed at retrieving the required clinical and epidemiological (local) data, identifying the uncertainties and estimating probabilities as discussed in the first part of this thesis. The second part builds on the available data, by putting them in an ethical perspective. In a moral deliberation session, involving all relevant stakeholders, the dilemma is evaluated. The framework does not aim to deliver 'the correct answer', but it structures the different aspects of antibiotic policy dilemmas in an era of antimicrobial resistance.

The ethical aspects involving antimicrobial therapy are complex, as the consequences of today's antibiotic policy transcend the individual patient, and even the current generation. It may be because of this complexity, that the ethical aspects often remain implicit in today's antibiotic guidelines on empiric therapy. Regardless of the method or framework that is used, guidelines should report thresholds, e.g. the resistance rate at which a change of antimicrobial class is recommended. More importantly, both the scientific and ethical considerations that lie at the base of the recommendations, should be made explicit. This transparency would enable local antibiotic policy makers, to translate international guidelines into local policy. Furthermore it may launch and support the debate on important questions, such as which degree of uncertainty is acceptable in empiric therapy, and how the interests of current and future generations relate to each other. As these questions are relevant for each dilemma on empiric antibiotic therapy, regardless of country and setting, more research should be directed on how to better integrate this ethical dilemma into antibiotic policy making.

CONCLUSIONS

In conclusion, it is essential that strategies are developed and implemented to optimize empiric therapy in those who need it, while minimizing exposure to broad-spectrum therapy in patients who will not benefit from it. Prediction tools to estimate the risk of BSI, antimicrobial resistance and/or complications, allow the targeting of antimicrobial regimens and support de-escalation strategies. These strategies should incorporate local epidemiology and the severity of the clinical syndrome, while balancing the importance of a match of empiric therapy against the pitfalls of overuse of broad-spectrum therapy. To design those strategies, thresholds should be determined on which uncertainties are -and are not- tolerable. To this aim ethics should be incorporated into antibiotic policy making explicitly.

REFERENCES

1. De Oliveira DMP, Forde BM, Kidd TJ, Harris PNA, Schembri MA, Beatson SA, et al. Antimicrobial Resistance in ESKAPE Pathogens. Clin Microbiol Rev. 2020;33(3).
2. Marturano JE, Lowery TJ. ESKAPE Pathogens in Bloodstream Infections Are Associated With Higher Cost and Mortality but Can Be Predicted Using Diagnoses Upon Admission. Open Forum Infect Dis. 2019;6(12):ofz503.
3. Pogue JM, Kaye KS, Cohen DA, Marchaim D. Appropriate antimicrobial therapy in the era of multidrug-resistant human pathogens. Clin Microbiol Infect. 2015;21(4):302-12.
4. Bogan C, Kaye KS, Chopra T, Hayakawa K, Pogue JM, Lephart PR, et al. Outcomes of carbapenem-resistant Enterobacteriaceae isolation: matched analysis. Am J Infect Control. 2014;42(6):612-20.
5. Hatch S. Uncertainty in medicine. BMJ. 2017;357:j2180.
6. Fabre V, Sharara SL, Salinas AB, Carroll KC, Desai S, Cosgrove SE. Does This Patient Need Blood Cultures? A Scoping Review of Indications for Blood Cultures in Adult Non-Neutropenic Inpatients. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.
7. Peralta G, Roiz MP, Sanchez MB, Garrido JC, Ceballos B, Rodriguez-Lera MJ, et al. Time-to-positivity in patients with Escherichia coli bacteraemia. Clin Microbiol Infect. 2007;13(11):1077-82.
8. Lamy B. Blood culture time-to-positivity: making use of the hidden information. Clin Microbiol Infect. 2019;25(3):268-71.
9. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2003;36(9):1103-10.
10. Aguilar-Guisado M, Espigado I, Martin-Pena A, Gudiol C, Royo-Cebrecos C, Falantes J, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematol. 2017;4(12):e573-e83.
11. Puerta-Alcalde P, Cardozo C, Suarez-Lledo M, Rodriguez-Nunez O, Morata L, Feher C, et al. Current time-to-positivity of blood cultures in febrile neutropenia: a tool to be used in stewardship de-escalation strategies. Clin Microbiol Infect. 2019;25(4):447-53.
12. Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica. 2013;98(12):1826-35.
13. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother. 2010;54(11):4851-63.
14. Simpkin AL, Schwartzstein RM. Tolerating Uncertainty - The Next Medical Revolution? The New England journal of medicine. 2016;375(18):1713-5.
15. Teixeira Rodrigues A, Roque F, Falcao A, Figueiras A, Herdeiro MT. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. International journal of antimicrobial agents. 2013;41(3):203-12.
16. Hall KH. Reviewing intuitive decision-making and uncertainty: the implications for medical education. Med Educ. 2002;36(3):216-24.

17. Roope LSJ, Buchanan J, Morrell L, Pouwels KB, Sivyer K, Mowbray F, et al. Why do hospital prescribers continue antibiotics when it is safe to stop? Results of a choice experiment survey. BMC Med. 2020;18(1):196.
18. Velasco E. A national cross-sectional study on socio-behavioural factors that influence physicians' decisions to begin antimicrobial therapy. Infection. 2011;39(4).
19. The National Institute for Health and Care Excellence. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NICE guideline 15). 2015. Available at: https://www.nice.org.uk/guidance/ng15