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Stewardship in sepsis

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ABSTRACT

Sepsis is the major cause of mortality from any infectious disease worldwide. The goals of antimicrobial stewardship are to achieve optimum clinical outcomes and to ensure cost effectiveness and minimum unintended consequences, including toxic effects, selection of pathogenic organisms, and resistance. The combination of inadequate diagnostic criteria for sepsis with the extraordinary time pressure to provide broad-spectrum antimicrobial therapy is troubling from a stewardship perspective. Use of empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral therapy, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation can lead to significant benefits for clinical outcomes, adverse events, and costs.

Key words: Sepsis; Stewardship; de-escalation

INTRODUCTION TO SEPSIS

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, is the major cause of mortality from any infectious disease worldwide [1]. The actual epidemiology of sepsis is currently unknown and extremely variable, since it depends on what we are analyzing, from incidence or prevalence to mortality [2]. Several factors influence, such as poorly classified records of different infectious pathologies and the concept of sepsis in a specific way, poorly or not designed for this purpose, or little information at a global and specific level [3].

A clinical syndrome that is this hard to define, is difficult to diagnose. It is estimated that around 50% of cases of sepsis based on coding are not correctly classified in the USA [4]. There is no one specific test to diagnose sepsis, and a number of different screening tools and biomarkers have been used. Traditional individual markers of sepsis, such as the total white cell count, neutrophil count, and C-reactive protein, lack the specificity to allow them to discriminate between those patients with an inflammatory response to trauma or surgery, for example, and those with an infection. In this sense, procalcitonin has shown to have the best accuracy to identify patients with invasive bacterial infections.

Despite many clinical trials, and the advent of modern intensive care, the mortality of severe sepsis and septic shock continues to be high. Good evidence of a mortality benefit in the early treatment of septic shock exists for two interventions: early goal-directed therapy and appropriate antibiotic therapy.

ANTIMICROBIAL STEWARDSHIP IN SEPSIS

The goals of antimicrobial stewardship (AS) are to achieve optimum clinical outcomes and to ensure cost effectiveness and minimum unintended consequences, including toxic effects, selection of pathogenic organisms, and resistance. However, sepsis represents a unique clinical dilemma with regard to AS. The concept AS is often considered to only include efforts to reduce or restrict use of expensive and broad-spectrum antimicrobials. The real exertion of and AS program should be on getting the right antimicrobial in the right dose to the right patient for the right amount of time [5] (figure 1). So, AS should pursue to achieve optimal clinical outcomes and to diminish drug related toxicity and other adverse events, with the minimum health-care related costs [6].

The combination of inadequate diagnostic criteria for sepsis with the extraordinary time pressure to provide broad-spectrum antimicrobial therapy is troubling from a stewardship

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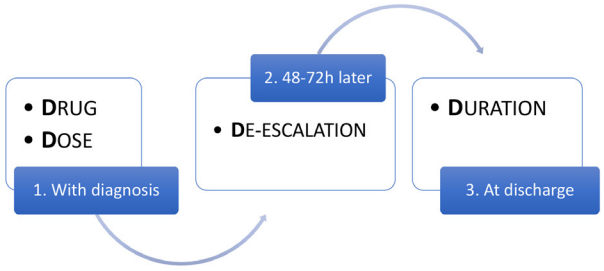

Figure 1 | **When can we do stewardship in sepsis?**

perspective [7]. We have to face several challenges. First, the diagnosis of severe sepsis may be delayed because of physicians or nurses may not identify the progression of sepsis and/or because some patients (e.j., hospitalized, immunosupressed,...) may not show obvious systemic manifestations of the process. Second, patients may have differences in the timing of their presentation and concurrent conditions confounding the diagnosis. Third, treatment may be delayed once the diagnosis is made [3]. An important epidemiological data is to know the origin of sepsis, which it is community in most cases, around 60-70% of whole cases, followed by hospital-acquired outside ICU in 20-30%, while cases of in ICU origin were the least frequent, around 5-9% [3]

MICROBIOLOGICAL DIAGNOSIS OF SEPSIS AND ANTIMICROBIAL STEWARDSHIP

Although approximately 40% of patients with sepsis are culture-negative, identification of a causative organism is essential to de-escalate antibiotics. A rapid response from the microbiology laboratory is a hallmark in hospital settings as in general terms close to 70% of the clinical decisions for the patient's management are based on laboratory results [8]. The first 3-6 hours after the clinical suspicion are critical to establish therapeutic measures that improve prognosis, therefore, a microbial diagnosis in less than 6 hours would undoubtedly benefit the optimal management of patients.

Despite no direct evidence that culture, especially blood culture, is beneficial for patients, indirect evidence supports this approach: de-escalation of antibiotic therapy and switching from intravenous to oral therapy had positive effects on clinical outcomes, adverse events, and costs. Blood cultures, aiming to detect viable microorganisms in blood, are still considered to be the reference standard for the microbiological diagnosis of bloodstream infections during sepsis [9]. However, this culture-based method suffers from important limitations, such as false-negative results because of ongoing antimicrobial therapy, and long time to positivity (usually from 12 hours to 72 hours). In of 50% of cases, bloodstream infections yielded a negative blood culture, and in sepsis even a higher number of blood cultures occur with negative results, which can delay the introduction of an adequate antimicrobial therapy [10]

It is much more interesting to have an etiological diagnosis of sepsis from the patient's direct blood rather than from positive blood cultures after blood incubation. The fastest strategy to identify microorganisms is by direct detection of DNA from blood, as this avoids the enrichment step in blood cultures. The turn-around time of these tests performed directly on blood samples ranges from 3 to 12 hours [1]. A pitfall of rapid molecular-based diagnostic tests for bacterial pathogens is that most of them usually provide little information on antimicrobial susceptibility.

The use of automated electronic sepsis alert system to improve sepsis management represents an area of active research. The widespread introduction of rapid response systems has led to the early identification and the initiation of early intervention to patients within the hospital system [11]. Although it is unlikely that computer programs would be able to tailor therapy in individual patients solely based on software, these programs could be used intelligently to identify key areas that need improvement.

TREATMENT OF SEPSIS AND ANTIMICROBIAL STEWARDSHIP

Timely administration of active antimicrobials has been a keystone of sepsis management even before it was included in the original Surviving Sepsis Campaign (SSC) guidelines [2]. The SSC Guidelines and clinical pathways are now available for several common infections, but the impact of the guidelines on prescribing is difficult to measure accurately. Guidelines recommend that empiric antimicrobial therapy should be based on likely pathogen and local/hospital resistance patterns. However, it is important to note that hospital antibiograms generated from inpatient may not mirror the septic population. Guideline uptake is more likely to be successful if they are tailored to match the local susceptibility patterns, and physicians are more likely to have confidence in guidelines if they are aware of the susceptibility patterns [12]. It is recommended that local susceptibility data should be updated at least annually.

Given the impact of early and broad-spectrum empirical therapy in several studies and the emphasis on this in international guidelines, there is a low threshold for initiating antibiotics in many patients with suspected infection. This has led to the widespread use of antibiotics in critically ill patients, which is often unnecessary or inappropriate. Enforcement of this concept in sepsis would be to cover all potential involved pathogens with the adequate antimicrobials since the first second. De-escalation will take place days later after the patient has been stabilized or when microbiological results (i.e., pathogen identification and definite antibiogram) are available. One area in which AS Programs need to focus on is de-escalation. De-escalation has been generally used in the context of narrowing therapy from broad-spectrum empirical to a nar-

row-spectrum pathogen-directed cover based upon laboratory results (i.e. drug de-escalation). Conceptually, reducing the dose (dose de-escalation), reducing the frequency (frequency de-escalation), switching from parenteral to oral therapy (route de-escalation), or switching from combination therapy to monotherapy are also examples of therapeutic streamlining that help reduce the consumption of antibiotics. [13] This needs systematic education, better diagnostic facilities, clinical microbiologist input, and pharmacy support.

Use of empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral therapy, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation (especially for *Staphylococcus aureus* bloodstream infection) can lead to signifi cant benefi ts for clinical outcomes, adverse events, and costs, although the quality of evidence is generally low [14].

Antibiotic resistance is a well recognized problem facing modern medicine and it is undeniable that in the last few years, levels of resistance have reached a tipping point. AS is now recognized as a formal strategy for curbing the upward trend in antibiotic resistance. Overuse and/or misuse of antimicrobials may result in selection of multidrug-resistant organisms, high rates of *Clostridium difficile* infections and adverse effects. Restrictive antibiotic policies have been associated with reduced resistance rates in most of the studies we assessed, but inconsistent relations between antibiotic use and resistance rates have been also found [14]. In several studies, increased prescriptions of non-restricted antibiotics were accompanied by concomitant increases in resistance rates.

WHAT ARE THE OBSTACLES THAT PREVENT GOOD STEWARDSHIP PROGRAMS?

The key areas that inform the AS Programs include patterns of prescribing, levels of antimicrobial resistance in a given setting, prescriber education, systematic collection of data in relation to prescribing, and a reliable measure of output. As opposed to structural and operational issues, use of education as an intervention is generally viewed as a medium to long-term strategy that underpins the AS Programs. But educational interventions can also be employed as an immediate tool with defined objectives such as steering the prescribing pattern in order to improve guidelines compliance as discussed above.

It is, thus, imperative to recognize that although the strategic tools can work at a macro level, clinician involvement is the key to successful implementation. The strategists need better clinical support, whereas the clinicians need better facilities in order to change their established practice. Infectious diseases physicians or clinical microbiologists are ideally and traditionally suited for such roles, and for successful implementation of AS Programs it would be vital to formally recognize their effort. This could include time allotment for such activities and also providing opportunity for gaining the Continuing Professional Development points for meetings. Lack of funding and personnel was described recently as a major barrier toward successful implementation of AS Programs [15] The crucial component of payment for physician time would need to be balanced with the cost savings expected as a result

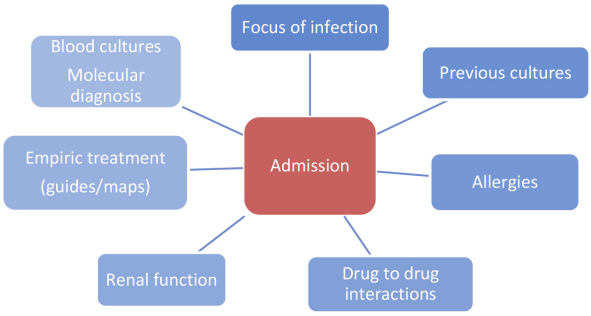

Figure 2 Opportunities of Antimicrobial Stewardship in the Management of Sepsis at admission

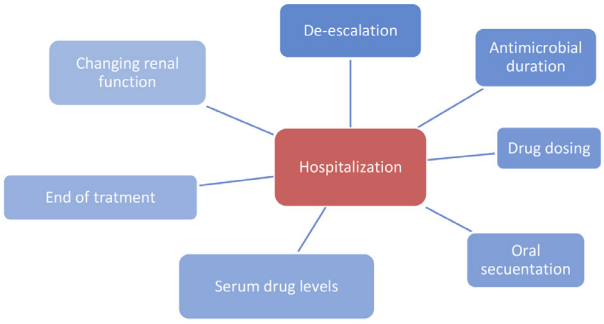

Figure 3 Opportunities of Antimicrobial Stewardship in the Management of Sepsis during hospitalization

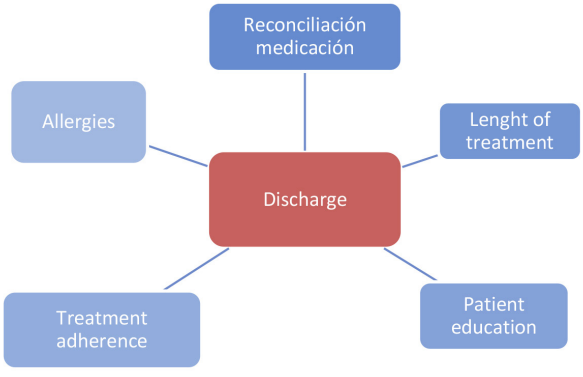

Figure 4 Opportunities of Antimicrobial Stewardship in the Management of Sepsis at discharge

of the AS Programs, and setting clear objectives would help achieve the goal. Rotating membership of AS Programs among colleagues in specialties other than infectious diseases and microbiology would make them feel involved in the strategic process.

Care bundles make it easier to implement the individual components by highlighting them under one goal and make it easier to measure the completeness of a given healthcare strategy. Such strategies have been documented to be successful because when these components are delivered together, their impact is more than when delivered individually (figures 2, 3 and 4).

CONCLUSIONS

The challenge for critical care physicians is thus to correctly diagnose sepsis and improve outcome while reducing antibiotic use. This can be done by adhering to local guidelines for empirical therapy, better risk for multidrug resistance assessment, optimized antibiotic dosing, and integration of rapid diagnostic techniques in the decision-making process.

It is recommended that hospitals implement an AS program to optimize use of antimicrobial agents, decrease antimicrobial resistance, and decrease rates of *Clostridium difficile* infection. there is clearly a need for more randomised multihospital trials to test the effectiveness of interventions on achieving stewardship outcomes and the subsequent effects on meaningful clinical outcomes. Specifically, robust demonstration of direct clinical benefits to individual patients would counteract the view of some health-care providers that stewardship interventions are designed for overall societal benefit, for example by reducing population-level rates of antimicrobial resistance or *Clostridium difficile* infection.

Integrating AS strategies in clinical practice can help upholding the best antibiotic empirical therapy while reducing antibiotic consumption. AS is a multidisciplinary policy and should be embraced by critical care physicians as a solution for balanced antibiotic use. The most effective AS intervention for sepsis will likely include a bundle composed of traditional quality improvement strategies (eg., education, audit, and feedback) combined with rapid diagnostic tests and adequate biomarkers.

QUESTIONS TO REFLECT

1. Are the goals of integrating antibiotic stewardship with the rapid treatment of severe sepsis mutually exclusive?

2. How can we balance rapid antimicrobial choices to select the best antibiotic while protecting members of the community from the further development of antimicrobial resistance

3. What are the practical benefits of a robust antibiotic stewardship program?

4. What are the obstacles that prevent good stewardship programs?

REFERENCES

1. Rello J, van Engelen TSR, Alp E, Calandra T, Cattoir V, Kern WV, et al. Towards precision medicine in sepsis: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect. 2018;24(12):1264-72. doi: 10.1016/j.cmi.2018.03.011. PubMed PMID: 29581049.
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10. doi: 10.1001/jama.2016.0287. PubMed PMID: 26903338; PubMed Central PMCID: PMCPMC4968574.
3. Candel FJ, Borges Sa M, Belda S, Bou G, Del Pozo JL, Estrada O, et al. Current aspects in sepsis approach. Turning things around. Rev Esp Quimioter. 2018;31(4):298-315. PubMed PMID: 29938972; PubMed Central PMCID: PMCPMC6172679.
4. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369(9):840-51. doi: 10.1056/NEJMra1208623. PubMed PMID: 23984731.
5. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Executive Summary: Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):1197-202. doi: 10.1093/cid/ciw217. PubMed PMID: 27118828.
6. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637. doi: 10.1097/CCM.0b013e31827e83af. PubMed PMID: 23353941.
7. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med. 2010;38(4):1045-53. doi: 10.1097/CCM.0b013e3181cc4824. PubMed PMID: 20048677.
8. Dumkow LE, Kenney RM, MacDonald NC, Carreno JJ, Malhotra MK, Davis SL. Impact of a Multidisciplinary Culture Follow-up Program of Antimicrobial Therapy in the Emergency Department. Infect Dis Ther. 2014;3(1):45-53. doi: 10.1007/s40121-014-0026-x. PubMed PMID: 25134811; PubMed Central PMCID: PMCPMC4108117.
9. Tziolos N, Giamarellos-Bourboulis EJ. Contemporary approaches to the rapid molecular diagnosis of sepsis. Expert Rev Mol Diagn. 2016;16(11):1201-7. doi: 10.1080/14737159.2016.1246958. PubMed PMID: 27728986.
10. Tabriz MS, Riederer K, Baran J, Jr., Khatib R. Repeating blood cultures during hospital stay: practice pattern at a teaching hospital and a proposal for guidelines. Clin Microbiol Infect. 2004;10(7):624-7. doi: 10.1111/j.1469-0691.2004.00893.x. PubMed PMID: 15214874.
11. Nelson JL, Smith BL, Jared JD, Younger JG. Prospective trial of real-time electronic surveillance to expedite early care of severe sepsis. Ann Emerg Med. 2011;57(5):500-4. doi: 10.1016/j.annemergmed.2010.12.008. PubMed PMID: 21227543.

12. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. JAMA. 2000;283(6):749-55. PubMed PMID: 10683053.

13. Vidaur L, Sirgo G, Rodriguez AH, Rello J. Clinical approach to the patient with suspected ventilator-associated pneumonia. Respir Care. 2005;50(7):965-74; discussion 74. PubMed PMID: 15972116.

14. Schuts EC, Hulscher M, Mouton JW, Verduin CM, Stuart J, Overdiek H, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(7):847-56. doi: 10.1016/S1473-3099(16)00065-7. PubMed PMID: 26947617.

15. Johannsson B, Beekmann SE, Srinivasan A, Hersh AL, Laxminarayan R, Polgreen PM. Improving antimicrobial stewardship: the evolution of programmatic strategies and barriers. Infect Control Hosp Epidemiol. 2011;32(4):367-74. doi: 10.1086/658946. PubMed PMID: 21460488.