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# Antibiotic Resistance

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## Introduction

Infectious diseases are a public health issue around the world, with bacterial, viral, parasitic, or fungal-related diseases responsible for 26% of mortality worldwide, and the remaining 74% attributed to non-communicable diseases (cardiovascular diseases, cancers, diabetes, trauma, etc.) (WHO 2018). The COVID-19 pandemic highlighted the high mortality of infectious diseases, with 5.94 million deaths in two years and nearly 18.2 million deaths worldwide (as measured by excess mortality) (COVID-19 Excess Mortality Collaborators 2022).

Among infectious diseases, sepsis is a major public health threat, responsible for 11 million deaths yearly (Rudd et al. 2020). Sepsis and septic shock are also the leading cause of death among children worldwide (Rhodes et al. 2017). Bacterial infections and sepsis can be effectively treated with antibiotics. However, the overuse of broad-spectrum antibiotics has led to bacterial antimicrobial resistance (AMR). Today, AMR is another major public health problem, with an estimated 4.95 million deaths associated with bacterial AMR in 2019 (Antibiotic Resistance Collaborators 2022). Sepsis and AMR together are responsible for more than 12.3 million deaths each year. The WHO has declared AMR one of the top ten global public health threats (WHO 2021).

# Pancreatic Stone Protein Biomarker for Sepsis, Anti-microbial Resistance and Nosocomial Infections

The problem of antimicrobial resistance and the use of a clinical decision score and point-of-care testing biomarkers, such as CRP and PSP, to help solve this problem.

Hospital Acquired Infections or Healthcare Associated Infections (HAIs) occur in 7-8% of hospitalised patients in Europe and 56% of patients in the ICU (Vincent et al. 2017). The main causes of nosocomial infections include bacterial AMR, lack of adherence to infection control and prevention procedures.

Bacterial infections can be complicated by sepsis and septic shock (Singer et al. 2017). In developing countries, the incidence of sepsis and septic shock is much higher than in high-income countries (Rudd et al. 2020). In addition, the administration of antibiotics is broad spectrum and leads to AMR (WHO 2011; Flandrin 2019; WHO 2020). For example, in India, the incidence rate of sepsis is the second highest in South Asia after Afghanistan (WHO 2011; Belagere 2020), and the incidence of nosocomial infection represents 11-60% (Choudhuri et al. 2017) of hospitalised patients. India also leads the world in human antibiotic use (Van Boeckel et al. 2014).

While the incidence of sepsis is higher in developing countries, the mortality rate is nearly 20-25% in developed countries. Sepsis-related costs in U.S. hospitals surpass US\$24 billion annually, making it the most expensive disease to manage (Torio and Moore 2016). Mortality from sepsis increases by about 8% per hour of delayed appropriate administration of antibiotics (Kumar et al. 2006). Hence, sepsis and septic shock can be prevented if diagnosed and treated early with appropriate treatment, in particular, antibiotics.

## Sepsis and Antimicrobial Resistance

The 2021 Surviving Sepsis Campaign (SSC) guidelines recommend starting antibiotics as soon as possible (ideally <45-60 minutes of recognition) (Evans et al. 2021). The determination of procalcitonin (PCT), with a specificity of 79% and sensitivity of 77% (Wacker et al. 2013), is not recommended because it has not demonstrated significant benefit for the patient. However, in a medical survey with 40 Swiss intensive care physicians, 92.3% test C-reactive protein (CRP), 84.6% PCT, 100% lactate and 89.7% leucocytes in case of suspicion of sepsis (Ventura 2021). Only 35.9% use the Sepsis-3 definition alone, while 34.2% calculate the qSOFA and 44.7% the SOFA. These data suggest that, in current practice, biomarkers are used more than scores. In addition to CRP and PCT, many biomarkers have been studied; however, none of them are included in the guidelines for early diagnosis of infection or sepsis because of the lack of consistent data.

There is a need to develop and optimise tools to manage sepsis and decrease the unnecessary use of antibiotics and the spread of AMR. Developing new antibiotics and searching for accurate solutions for early diagnosis of sepsis are also a priority. One possible solution could be using biomarkers combined with clinical decision support algorithms. The positive predictive value of biomarkers/algorithms could allow judicious and timely initiation of antibiotics, while

negative predictive values could indicate that antibiotics need not be administered.

Several research projects are already under way. For example, a point-of-care testing (POCT) solution using CRP and PCT has been integrated into algorithms. The e-POCT solution is an innovative electronic algorithm using host biomarker POCTs, including CRP and PCT. It could potentially improve clinical outcomes among children with febrile illnesses while reducing the use of antibiotics through improved identification and better targeting of children in need of antibiotics (Keitel et al. 2017).

### Pancreatic Stone Protein

Another possible diagnostic tool could be a solution based on clinical algorithms and the use of biomarkers with the combination of CRP and a new early biomarker of sepsis, the Pancreatic Stone Protein (PSP). Two literature reviews (Eggimann et al. 2019; Fidalgo et al. 2022) suggest that PSP could be an innovative tool for the detection of pre-symptomatic sepsis. PSP is a 16 kDa C-type lectin protein produced mostly by the pancreas and the intestine. PSP is measured in less than 10 minutes, from a drop of capillary or venous whole blood, at the point-of-care (POC) by an innovative nanofluidic technology (abioSCOPE, Abionic, Epalinges, Switzerland) CE certified since January 2020. PSP can be used to diagnose sepsis even in severe inflammatory states, such as in trauma patients (Keel et al. 2009; Klein et al. 2020a), postoperative patients (Klein et al. 2020a; Klein et al. 2015), severely burned patients (Klein et al. 2020b), and in acute respiratory distress syndrome (ARDS) after inhalation (Klein et al. 2020c).

A meta-analysis shows that PSP is more

sensitive and specific than CRP and PCT for the diagnosis of infection. The combination of CRP with PSP further enhances its accuracy with higher sensitivity and specificity for discriminating infection from non-infection (Prazak et al. 2021). PSP increases early, nearly 48-72 hours before manifestation of clinical suspicion of nosocomial sepsis, organ dysregulated response onset and elevation of CRP and PCT. Findings from a study conclude that "while the diagnostic accuracy of PSP, CRP and PCT for sepsis were similar in this cohort, serial PSP measurement demonstrated an increase of this marker the days preceding the onset of signs necessary to clinical diagnose sepsis" (Pugin et al. 2021). The kinetics of PSP allow early diagnosis of nosocomial sepsis, even before manifestation of clinical signs and symptoms. Daily measurement of this biomarker is, therefore, routinely proposed in the ICU (Pugin et al. 2021). The CRP/PSP combination is also more specific and sensitive than CRP, PCT, and PSP alone for diagnosing sepsis. Moreover, CRP and PSP dosages are accessible from a drop of blood in less than 10 minutes at the POC.

### Conclusion

Overall, it is evident that there is a need for better tools to guide the initiation of antibiotics in managing sepsis. These tools can also lead to the appropriate use of antibiotics and help decrease the burden of AMR. Using PSP in combination with other biomarkers (CRP) can provide a useful and practical approach in patients presenting with sepsis with a major impact on AMR. Moreover, integrating this combination of biomarkers (CRP/PSP) with a clinical decision support algorithm could represent an innovative solution to help overcome the

challenges related to sepsis and AMR. The savings for public health would also be major, and an estimated 1 million lives could be saved by 2030 (Ventura 2020). Hence, the use of a clinical decision score and POCT biomarkers, such as CRP and PSP, can help solve several major health problems: sepsis, AMR, and nosocomial infections. ■

### Key Points

- Sepsis is a major public health threat and responsible for 11 million deaths annually.
- Antimicrobial resistance (AMR) is another major public health problem, with an estimated 4.95 million deaths associated with bacterial AMR in 2019.
- The WHO has declared AMR one of the top ten global public health threats facing humanity.
- The 2021 Surviving Sepsis Campaign (SSC) guidelines recommend starting antibiotics as soon as possible, ideally within one hour of recognition.
- There is a need to develop and optimise tools to manage sepsis and decrease the unnecessary use of antibiotics and the spread of AMR.
- The use of biomarkers such as pancreatic stone protein (PSP), a new biomarker shown to detect pre-symptomatic sepsis up to 72 hours before the current standard of care, could be used in combination with clinical decision support algorithms as a possible solution to improve the diagnosis of sepsis and ultimately help overcome the global challenges related to sepsis and AMR.

### Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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