

A Global Declaration on Appropriate Use of Antimicrobial Agents across the Surgical Pathway

Global Alliance for Infections in Surgery Working Group

Abstract

This declaration, signed by an interdisciplinary task force of 234 experts from 83 different countries with different backgrounds, highlights the threat posed by antimicrobial resistance and the need for appropriate use of antibiotic agents and antifungal agents in hospitals worldwide especially focusing on surgical infections. As such, it is our intent to raise awareness among healthcare workers and improve antimicrobial prescribing. To facilitate its dissemination, the declaration was translated in different languages.

ANTIMICROBIAL RESISTANCE (AMR) has emerged as one of the principal public health problems of the 21st century. This has resulted in a public health crisis of international concern, which threatens the practice of modern medicine, animal health, and food security. The substantial problem of AMR is especially relevant to antibiotic resistance (ABR), although antifungal resistance is increasing at an alarming rate. Although the phenomenon of ABR can be attributed to many factors, there is a well-established relationship between antibiotic prescribing practices and the emergence of resistant bacteria.

This declaration, signed by an interdisciplinary task force of 234 experts from 83 different countries with different backgrounds, highlights the threat posed by AMR and the need for appropriate use of antibiotic agents and antifungal agents in hospitals worldwide especially focusing on surgical infections. This declaration is promoted by the Global Alliance for Infections in Surgery and the World Society of Emergency Surgery (WSES). It is endorsed by the Surgical Infection Society (SIS), the Surgical Infection Society Europe (SIS-E), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Antimicrobial stewardship (ES-GAP) and Study Group for Infections in Critically Ill Patients (ESGCIP), the European Confederation of Medical Mycology (ECMM), the World Alliance Against Antibiotic Resistance (WAAR), the British Society for Antimicrobial Chemotherapy (BSAC), the French Society of Anesthesia & Intensive Care Medicine (SFAR), the Italian Society of Anesthesiology, Analgesia, Resuscitation and Intensive Therapy (SIAARTI), the South African Society of Clinical Microbiology (SASCM), the Italian Society of Anti-Infective Therapy (SITA), and the Italian Group for Antimicrobial Stewardship (GISA).

Antibiotic and Antifungal Resistance

Antibiotic resistance is one of the greatest threats to public health, sustainable development, and security worldwide. Its prevalence has increased alarmingly over the past decades. In 2008, the acronym “ESKAPE” pathogens, which refers to *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species was proposed to highlight those pathogens about which ABR is of particular concern and to emphasize which bacteria increasingly “escape” the effects of antibiotics [1]. These organisms are increasingly multi-drug- (MDR), extensive-drug- (XDR), and pan-drug-resistant (PDR), and this process is accelerating globally [2,3].

Although antibiotic-resistant infections are a widely recognized public health threat, less is known about the burden of antifungal-resistant infections. The frequency of fungal infections has increased in recent years, largely because of the increasing size of the at-risk population, which includes cancer patients, transplant recipients, patients with human immunodeficiency virus infection, and other patients who receive immunosuppressive therapy. In addition, they are relatively common in critically ill patients and are associated with considerable morbidity and death. In this regard, antifungal resistance is becoming increasingly problematic, particularly for *Candida glabrata* and *Aspergillus fumigatus*. Recently, a new MDR species, *C. auris*, emerged causing persistent multi-regional outbreaks. While some species of *Candida* are inherently resistant to certain antifungal agents, in others, acquired resistance occurs via selection of mutations in existing genes, particularly in units with high

antifungal consumption [4]. This can impact seriously the outcomes of patients with invasive candidiasis. The problem will likely continue to evolve unless greater attention is given to measures to prevent and control the spread of resistant *Candida* spp.

Combating resistance has become a top priority for global policy makers and public health authorities. New mechanisms of resistance continue to emerge and spread globally, threatening our ability to manage common infections [5]. Antibacterial and antifungal use in animal and agricultural industries aggravates selective pressure on microbes. A One Health approach is required urgently. The burden of ABR is difficult to quantify in some regions of the world, because enhanced surveillance requires personnel, equipment, and financial resources that are not always available [6]. The worldwide impact of ABR is significant, however, in terms of economic and patient outcomes, because of untreatable infections or those necessitating antibiotic agents of last resort (such as colistin) leading to increased length of hospital stay, morbidity, death, and treatment cost.

Misuse and Overuse of Antibiotic Agents

Antibiotic agents can be lifesaving when treating patients with bacterial infections but are often used inappropriately, specifically when unnecessary or when administered for excessive durations or without consideration of pharmacokinetic principles. Large variations in antibiotic consumption exist between countries, and while excessive use remains a major problem in some areas of the world, elsewhere there is lack of access to many antimicrobial agents. Antibiotic resistance is a natural phenomenon that occurs as microbes evolve. Human activities have accelerated the pace at which bacteria develop and disseminate resistance, however. Inappropriate use of antibiotic agents in humans and food-producing animals, as well as poor infection prevention and control (IPC) practices, contribute to the development and spread of ABR.

Raising Awareness to Combat ABR

In line with a One Health approach, raising awareness of ABR by education and dissemination of information to stakeholders is an important factor in changing behaviors. Efforts must be aimed at the general public, healthcare professionals, food producing farmers, civil society organizations, and policy makers. An effective and cost-effective strategy to reduce ABR should involve a multi-faceted approach aimed at optimizing antibiotic use, strengthening surveillance and IPC, and improving patient and clinician education regarding the appropriate use of antibiotic agents. Although the current magnitude of the problem and its extent in both the community and the hospital adds to the complexity of any intervention, these are still necessary because healthcare workers play a central role in preventing the emergence and spread of resistance.

Improving Antibiotic Prescribing Behaviors

Appropriate use of antibiotic agents should be integral to good clinical practice and standards of care [7,8]. Physicians should be aware of their role and responsibility for main-

taining the effectiveness of current and future antibiotic agents specifically by:

- Following locally developed customized antibiotic guidelines and clinical pathways
- Supporting and enhancing IPC including correct hand hygiene protocols
- Supporting and enhancing surveillance of ABR and antibiotic consumption
- Prescribing and dispensing antibiotic agents only when they are truly required
- Identifying and controlling the source of infection
- Prescribing and dispensing appropriate antibiotic agents with adequate dosages—i.e., administration of antibiotic agents according to pharmacokinetic-pharmacodynamic (PK-PD) principles
- Re-assessing treatment when culture results are available
- Using the shortest duration of antibiotic agents based on evidence
- Educating healthcare workers and staff how to use antibiotic agents wisely

Antibiotic Stewardship Programs

Hospital-based programs dedicated to improving antibiotic use, commonly referred to as Antimicrobial Stewardship Programs (ASPs), can both optimize the management of infections and reduce adverse events associated with antibiotic use [8,9]. Of note, a recent systematic review and meta-analysis demonstrated that ASPs significantly reduce the incidence of infections and colonization with antibiotic-resistant bacteria and *Clostridium difficile* infections in hospital inpatients [10]. Therefore, every hospital worldwide should utilize existing resources to create an effective multidisciplinary team. The preferred means of improving antibiotic stewardship should involve a comprehensive program that incorporates collaboration between various specialties within a healthcare institution including infectious disease specialists, hospital pharmacists, clinical pharmacologists, administrators, epidemiologists, IPC specialists, microbiologists, surgeons, anesthesiologists, intensivists, and underutilized but pivotal stewardship team members—the surgical, anesthetic, and intensive care nurses in our hospitals.

The ASP policies should be based on both international/national antibiotic guidelines and tailored to local microbiology and resistance patterns. Facility-specific treatment recommendations, based on guidelines and local formulary options promoted by the APS team, can guide clinicians in antibiotic agent selection and duration for the most common indications for antibiotic use. Standardizing a shared protocol of antibiotic prophylaxis should represent the first step of any ASP. Because physicians are responsible primarily for the decision to use antibiotic agents, educating them and changing the attitudes and knowledge that underlie their prescribing behavior are crucial for improving antibiotic prescription.

Education is fundamental to every ASP. A range of factors such as diagnostic uncertainty, fear of clinical failure, time pressure, or organizational contexts can complicate prescribing decisions. Because of cognitive dissonance (recognizing that an action is necessary but not implementing it),

however, changing prescribing behavior is extremely challenging [11]. Efforts to improve educational programs are thus required, and this should be complemented preferably by active interventions such as prospective audits and feedback to clinicians to stimulate further change [12]. It is also crucial to incorporate fundamental ASP [13] and IPC principles in under- and post-graduate training at medical faculties to equip young physicians and other healthcare professionals with the required confidence, skills, and expertise in the field of antibiotic management.

The principles for appropriate prophylactic and therapeutic use of antibiotic agents in surgical procedures are summarized below.

Please, use antibiotics appropriately and play an active role in combating antibiotic resistance. Join us now, as we embark on this global cause, by pledging support for this declaration and accepting responsibility for maintaining the effectiveness and longevity of current and future antibiotic agents.

Principles of Appropriate Antibiotic Prophylaxis in Surgical Procedures

1. Antibiotic agents alone are unable to prevent surgical site infections. Strategies to prevent surgical site infections should always include attention to:
 - IPC strategies including correct and compliant hand hygiene practices
 - Meticulous surgical techniques and minimization of tissue trauma
 - Hospital and operating room environments
 - Instrument sterilization processes
 - Peri-operative optimization of patient risk factors
 - Peri-operative temperature, fluid, and oxygenation management
 - Targeted glycemic control
 - Appropriate management of surgical wounds
2. Antibiotic prophylaxis should be administered for operative procedures that have a high rate of post-operative surgical site infection, or when foreign materials are implanted.
3. Antibiotic agents given as prophylaxis should be effective against the aerobic and anaerobic pathogens most likely to contaminate the surgical site—i.e., gram-positive skin commensals or normal flora colonizing the incised mucosae.
4. Antibiotic prophylaxis should be administered within 120 minutes before the incision. Administration of the first dose of antibiotic agents beginning within 30 to 60 minutes before surgical incision, however, is recommended for most antibiotic agents (e.g., cefazolin), to ensure adequate serum and tissue concentrations during the period of potential contamination. Obese patients ≥ 120 kg require higher doses of antibiotic agents.
5. A single dose generally is sufficient. Additional antibiotic doses should be administered intra-operatively for procedures >2 –4 hours (typically where duration exceeds two half-lives of the antibiotic) or with associated significant blood loss (>1.5 L).
6. There is no evidence to support the use of post-operative antibiotic prophylaxis.

7. Each institution is encouraged to develop guidelines for proper surgical prophylaxis.

Principles of Appropriate Antibiotic Therapy in Surgical Procedures

1. The source of infection should always be identified and controlled as soon as possible.
2. Antibiotic empiric therapy should be initiated after a treatable surgical infection has been recognized, because microbiologic data (culture and susceptibility results) may not be available for up to 48–72 hours to guide targeted therapy.
3. In critically ill patients, empiric broad-spectrum therapy to cover the most likely pathogens should be initiated as soon as possible after a surgical infection has been recognized. Empiric antimicrobial therapy should be narrowed once culture and susceptibility results are available and adequate clinical improvement is noted.
4. Empiric therapy should be chosen on the basis of local epidemiology, individual patient risk factors for MDR bacteria and *Candida* spp., clinical severity, and infection source.
5. Specimens for microbiologic evaluation from the site of infection are always recommended for patients with hospital-acquired or with community-acquired infections at risk for resistant pathogens (e.g., previous antimicrobial therapy, previous infection or colonization with a MDR, XDR, and PDR pathogen) and in critically ill patients. Blood cultures should be performed before the administration of antibiotic agents in critically ill patients.
6. The antibiotic dose should be optimized to ensure that PK-PD targets are achieved. This involves prescribing an adequate dose, according to the most appropriate and right method and schedule to maximize the probability of target attainment.
7. The appropriateness and need for antimicrobial treatment should be re-assessed daily.
8. Once source control is established, short courses of antibiotic therapy are as effective as longer courses regardless of signs of inflammation.
 - Intra-abdominal infection—four days are as effective as eight days in moderately ill patients [14]
 - Blood stream infection—five to seven days are as effective as seven to 21 days for most patients [15]
 - Ventilator associated pneumonia—eight days are as effective as 15 days [16,17].
9. Failure of antibiotic therapy in patients having continued evidence of active infection may require a re-operation for a second source control intervention.
10. Biomarkers such as procalcitonin may be useful to guide duration and cessation of antibiotic therapy in critically ill patients.
11. Clinicians with advanced training and clinical experience in surgical infections should be included in the care of patients with severe infections.
12. The IPC measures combined with ASPs should be implemented in surgical departments. These interventions and programs require regular, systematic monitoring to assess compliance and efficacy.

- Monitoring of antibiotic consumption should be implemented and feedback provided to all ASP team members regularly (e.g., every three to six months) along with resistance surveillance data and outcome measures.

The documents translated into French, Spanish, Portuguese, Chinese, Arabic, Russian, German, Japanese, Italian and Greek are included in the Supplementary Material; see online only supplementary material at www.liebertpub.com/sur.

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Acknowledgments

Authors

Members of the Global Alliance for Infections in Surgery Working Group are:

Massimo Sartelli,¹ Yoram Kluger,² Luca Ansaloni,³ Jean Carlet,⁴ Adrian Brink,⁵ Timothy C. Hardcastle,⁶ Ashish Khanna,⁷ Alain Chicom-Mefire,⁸ Jesús Rodríguez-Baño,⁹ Dilip Nathwani,¹⁰ Marc Mendelson,¹¹ Richard R. Watkins,¹² Celine Pulcini,¹³ Bojana Beović,¹⁴ Addison K. May,¹⁵ Kamal MF. Itani,¹⁶ John E. Mazuski,¹⁷ Donald E. Fry,¹⁸ Federico Coccolini,³ Kemal Raşa,¹⁹ Philippe Montravers,²⁰ Christian Eckmann,²¹ Lilian M. Abbo,²² Salisu Abubakar,²³ Fikri M. Abu-Zidan,²⁴ Abdulrashid Kayode Ade-sunkanmi,²⁵ Majdi N. Al-Hasan,²⁶ Asma A Althani,²⁷ Jorge Eduardo Alvarenga Ticas,²⁸ Shamshul Ansari,²⁹ Rashid Ansumana,³⁰ André Ricardo Araujo da Silva,³¹ Goran Augustin,³² Miklosh Bala,³³ Zsolt J Balogh,³⁴ Oussema Barakat,³⁵ Matteo Bassetti,³⁶ Giovanni Bellanova,³⁷ Marcelo A. Beltran,³⁸ Ofir Ben-Ishay,² Walter L. Biffl,³⁹ Marja A. Boermeester,⁴⁰ Stephen M. Brecher,⁴¹ Juan Bueno,⁴² Miguel A. Cainzos,⁴³ Kelly Cairns,⁴⁴ Adrian Camacho-Ortiz,⁴⁵ Marco Ceresoli,³ Sujith J. Chandly,⁴⁶ Jill R. Cherry-Bukowiec,⁴⁷ Roberto Cirocchi,⁴⁸ Elif Colak,⁴⁹ Antonio Corcione,⁵⁰ Oliver A. Cornely,⁵¹ Francesco Cortese,⁵² Yunfeng Cui,⁵³ Daniel Curcio,⁵⁴ Dimitris Damaskos,⁵⁵ Koray Daş,⁵⁶ Samir Delibegovic,⁵⁷ Zaza Demetrashvili,⁵⁸ Belinda De Simone,⁵⁹ Hamilton Petry de Souza,⁶⁰ Jan De Waele,⁶¹ Sameer Dhingra,⁶² Jose J. Diaz,⁶³ Isidoro Di Carlo,⁶⁴ Francesco Di Marzo,⁶⁵ Salomone Di Saverio,⁶⁶ Agron Dogjani,⁶⁷ Gereltuya Dorj,⁶⁸ Laurent Dortet,⁶⁹ Therese M. Duane,⁷⁰ Herve Dupont,⁷¹ Valery N. Egiev,⁷² Hani O. Eid,⁷³ Mutasim Elmangory,⁷⁴ Hany El-Sayed Marei,²⁷ Mushira Abdulaziz Enani,⁷⁵ Kevin Escandón-Vargas,⁷⁶ Mario P Faro Junior,⁷⁷ Paula Ferrada,⁷⁸ Domitilla Foghetti,⁷⁹ Esteban Foianini,⁸ Gustavo P. Fraga,⁸¹ Sabrina Frattina,⁸² Chinmay Gandhi,⁸³ Gianni Gattuso,⁸⁴ Eleni Giamarellou,⁸⁵ Wagih Ghnnam,⁸⁶ George Gkiokas,⁸⁷ Massimo Girardis,⁸⁸ Debbie A. Goff,⁸⁹ Carlos Augusto Gomes,⁹⁰ Harumi Gomi,⁹¹ Rosio Isabel Guerra Gronerth,⁹² Xavier Guirao,⁹³ Manuel Guzman-Blanco,⁹⁴ Mainul Haque,⁹⁵ Andreas Hecker,⁹⁶ Markus Hell,⁹⁷ Torsten Herzog,⁹⁸ Lauri Hicks,⁹⁹ Reinhold Kafka-Ritsch,¹⁰⁰ Lillian S. Kao,¹⁰¹ Souha S Kanj,¹⁰² Lewis J Kaplan,¹⁰³ Garima Kapoor,¹⁰⁴ Aleksandar Karamarkovic,¹⁰⁵ Jeffrey Kashuk,¹⁰⁶ Jakob Kenig,¹⁰⁷ Faryal Khamis,¹⁰⁸ Vladimir Khokha,¹⁰⁹ Ronald Kiguba,¹¹⁰ Andrew W. Kirkpatrick,¹¹¹ Hartwig Körner,¹¹² Kaoru Koike,¹¹³ Kenneth YY. Kok,¹¹⁴ Kateryna Kon,¹¹⁵ Victor Kong,¹¹⁶ Kenji Inaba,¹¹⁷ Orestis Ioannidis,¹¹⁸ Arda Isik,¹¹⁹ Katia Iskandar,¹²⁰ Maurizio Labbate,¹²¹ Francesco M. Labricciosa,¹²² Katrien Lagrou,¹²³ Leonel Lagunes,¹²⁴ Rifat Latifi,¹²⁵ Kostas Lasithiotakis,¹²⁶ Ramanan Laxminarayan,¹²⁷ Jae Gil Lee,¹²⁸ Marc Leone,¹²⁹ Ari Leppäniemi,¹³⁰ Yousheng Li,¹³¹ Stephen Y Liang,¹³² Kui-Hin Liao,¹³³ Andrew Litvin,¹³⁴ Tonny Loho,¹³⁵ Warren Lowman,¹³⁶ Gustavo M. Machain,¹³⁷ Ronald V. Maier,¹³⁸ Ramiro Manzano-Nunez,¹³⁹ Athanasios Marinis,¹⁴⁰ Cristina Marmorale,¹⁴¹ Ignacio Martin-Loeches,¹⁴² Sanjay Marwah,¹⁴³ Emilio Maseda,¹⁴⁴ Michael McFarlane,¹⁴⁵ Renato Bessa de Melo,¹⁴⁶ Maria Rita Melotti,¹⁴⁷ Ziad Memish,¹⁴⁸ Dominik Mertz,¹⁴⁹ Cristian Mesina,¹⁵⁰ Francesco Menichetti,¹⁵¹ Shyam Kumar Mishra,¹⁵² Giulia Montori,³ Ernest E. Moore,¹⁵³ Frederick A. Moore,¹⁵⁴ Noel Naidoo,¹⁵⁵ Lena Napolitano,¹⁵⁶ Ionut Negoi,¹⁵⁷ David P. Nicolau,¹⁵⁸ Ioannis Nikolopoulos,¹⁵⁹ Carl Erik Nord,¹⁶⁰ Richard Ofori-Asenso,¹⁶¹ Iyiade Olaoye,¹⁶² Abdelkarim H Omari,¹⁶³ Carlos A. Ordoñez,¹⁶⁴ Mouaqit Oudii,¹⁶⁵ Abdoul-Salam Ouedraogo,¹⁶⁶ Leonardo Pagani,¹⁶⁷ José Artur Paiva,¹⁶⁸ Jose Gustavo Parreira,¹⁶⁹ Francesco Pata,¹⁷⁰ Jorge Pereira,¹⁷¹ Nuno R Pereira,¹⁷² Nicola

Petrosillo,¹⁷³ Edoardo Picetti,¹⁷⁴ Tadeja Pintar,¹⁷⁵ Alfredo Ponce-de-Leon,¹⁷⁶ Zagorka Popovski,¹⁷⁷ Garyphallia Poulakou,¹⁷⁸ Jacobus Preller,¹⁷⁹ Adrián Puello Guerrero,¹⁸⁰ Guntars Pupelis,¹⁸¹ Martha Quiodettis,¹⁸² Timothy M Rawson,¹⁸³ Martin Reichert,⁹⁵ Konrad Reinhart,¹⁸⁴ Miran Rems,¹⁸⁵ Jordi Rello,¹⁸⁶ Sandro Rizoli,¹⁸⁷ Jason Roberts,¹⁸⁸ Ines Rubio-Perez,¹⁸⁹ Etienne Ruppé,¹⁹⁰ Boris Sakakushev,¹⁹¹ Ibrahima Sall,¹⁹² Hossein Samadi Kafil,¹⁹³ James Sanders,¹⁹⁴ Norio Sato,¹⁹⁵ Robert G Sawyer,¹⁹⁶ Thomas Scalea,¹⁹⁷ Rodolfo Scibé,¹ Luigia Scudeller,¹⁹⁸ Helmut Segovia Lohse,¹³⁷ Gabriele Sganga,¹⁹⁹ Nusrat Shafiq,²⁰⁰ Jay N Shah,²⁰¹ Patrizia Spigaglia,²⁰² Shanoo Suroowan,²⁰³ Constantinos Tsioutis,²⁰⁴ Costi D Sifri,²⁰⁵ Boonying Siribumrungwong,²⁰⁶ Michael Sugrue,²⁰⁷ Peep Talving,²⁰⁸ Boun Kim Tan,²⁰⁹ Antonio Tarasconi,²¹⁰ Carlo Tascini,²¹¹ Jonathan Tilsed,²¹² Jean-François Timsit,²¹³ Mario Tumbarello,²¹⁴ Ngo Tat Trung,²¹⁵ Jan Ulrych,²¹⁶ Selman Uranues,²¹⁷ George Velmahos,²¹⁸ Andrés G. Vereczkei,²¹⁹ Pierluigi Viale,²²⁰ Jordi Vila Estape,²²¹ Claudio Viscoli,²²² Florian Wagenlehner,²²³ Brian J. Wright,²²⁴ Yonghong Xiao,²²⁵ Kuo-Ching Yuan,²²⁶ Sanoop K Zachariah,²²⁷ Jean Ralph Zahar,²²⁸ Paulo Mergulhão,¹⁶⁸ Fausto Catena.²¹⁰

Author Affiliations

1. Department of Surgery, Macerata Hospital, Macerata, Italy.
2. Department of General Surgery, Division of Surgery, Rambam Health Care Campus, Haifa, Israel.
3. General Surgery Department, Papa Giovanni XXIII Hospital, Bergamo, Italy.
4. President of World Alliance against Antibiotics Resistance, Paris, France
5. Department of Clinical Microbiology, Ampath National Laboratory Services, Milpark Hospital, Johannesburg, South Africa, and Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, Cape Town, South Africa.
6. Trauma Service, Inkosi Albert Luthuli Central Hospital and Department of Surgery, Nelson R Mandela School of Clinical Medicine, Durban, South Africa.
7. Center for Critical Care, Anaesthesiology Institute and Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio, United States of America.
8. Department of Surgery and Obstetrics/Gynaecology, University of Buea, Cameroon.
9. Unidad Clínica Intercentros de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospitales Universitarios Virgen Macarena y Virgen del Rocío-IbIS and Departamento de Medicina, Universidad de Sevilla, Seville, Spain.
10. Ninewells Hospital and Medical School, Dundee, United Kingdom.
11. Division of Infectious Diseases & HIV Medicine, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa.
12. Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, Ohio, and Department of Medicine, Northeast Ohio Medical University, Rootstown, Ohio, United States of America.
13. Lorraine University, EA 4360 APEMAC, Nancy, France; Nancy University Hospital, Infectious Diseases Department, Nancy, France.
14. University Medical Centre Ljubljana, Slovenia; Faculty of Medicine, University of Ljubljana, Slovenia.
15. Division of Trauma and Surgical Critical Care, Vanderbilt University Medical Center, Nashville, Tennessee, United States of America.
16. Department of Surgery, VA Boston Health Care System, Boston University and Harvard Medical School, Boston, Massachusetts, United States of America.
17. Department of Surgery, School of Medicine, Washington University, Saint Louis, Missouri, United States of America.
18. Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois; University of New Mexico School of Medicine, Albuquerque, New Mexico, United States of America.
19. Department of Surgery, Anadolu Medical Center, Kocaali, Turkey.
20. Anesthesiology and Critical Care Medicine, Paris Diderot Sorbonne Cite University, Bichat-Claude Bernard University Hospital, HUPNSV, Paris, France.
21. Department of General, Visceral & Thoracic Surgery, Academic Hospital of Medical University Hannover, Peine, Germany.
22. Division of Infectious Diseases, Jackson Health System, University of Miami Miller School of Medicine, Miami, Florida, United States of America, Department of Nursing Science, Bayero University Kano, Nigeria.
23. Department of Surgery, College of Medicine and Health Sciences, UAE University, Al-Ain, United Arab Emirates.
24. Department of Surgery, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria.
25. Department of Medicine, Division of Infectious Diseases, University of South Carolina School of Medicine, Columbia, South Carolina, United States of America.
26. Biomedical Research Center, Qatar University, Doha, Qatar.
27. Emergency Unit, Hospital Nacional Rosales, San Salvador, El Salvador.
28. Department of Environmental and Preventive Medicine, Faculty of Medicine, Oita University, Oita, Japan, and Department of Microbiology, Chitwan Medical College, Bharatpur, Nepal.
29. Centre for Neglected Tropical Diseases, Liverpool School of Tropical Medicine, University of Liverpool, and Mercy Hospital Research Laboratory, Njala University, Bo, Sierra Leone.
30. Infection Control Committee, Prontobaby Hospital da Criança, Rio de Janeiro, Brazil.
31. Department of Surgery, University Hospital Centre, Zagreb, Croatia.
32. Trauma and Acute Care Surgery Unit, Hadassah Hebrew University Medical Center, Jerusalem, Israel.
33. Department of Traumatology, John Hunter Hospital and University of Newcastle, Newcastle, New South Wales, Australia.
34. Department of Surgery, Bizerte Hospital, Bizerte, Tunisia.
35. Infectious Diseases Division, Santa Maria Misericordia University Hospital, Udine, Italy.
36. Department of Surgery, S.S. Annunziata Hospital, Taranto, Italy.
37. Department of General Surgery, Hospital San Juan de Dios de La Serena, La Serena, Chile.
38. Acute Care Surgery, The Queen's Medical Center, Honolulu, Hawaii, United States of America.
39. Department of Surgery, Academic Medical Centre, Amsterdam, Netherlands.
40. Department of Pathology and Laboratory Medicine, VA Boston HealthCare System, and Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston, Massachusetts, United States of America.
41. Fundación Centro de Investigación de Bioprospección y Biotecnología de la Biodiversidad (BIOLABB), Colombia.
42. Department of Surgery, Hospital Clínico Universitario, Santiago de Compostela, Spain.
43. Pharmacy Department, Alfred Health, Melbourne, Victoria, Australia.
44. Hospital Epidemiology and Infectious Diseases, Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico.
45. Department of Pharmacology & Clinical Pharmacology, Christian Medical College, Vellore, India.
46. Division of Acute Care Surgery, Department of Surgery, University of Michigan, Ann Arbor, Michigan, United States of America.
47. Department of General and Oncologic Surgery, University of Perugia, Terni, Italy.
48. Department of General Surgery, Health Sciences University, Samsun Training and Research Hospital, Samsun, Turkey.
49. Anesthesia and Intensive Care Unit, AORN dei Colli Vincenzo Monaldi Hospital, Naples, Italy.
50. Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Department I of Internal Medicine, Clinical Trials Centre Cologne (ZKS Köln), German Centre for Infection Research (DZIF), University of Cologne, Cologne, Germany.
51. Emergency Surgery Unit, San Filippo Neri's Hospital, Rome, Italy.
52. Department of Surgery, Tianjin Nankai Hospital, Nankai Clinical School of Medicine, Tianjin Medical University, Tianjin, China.
53. Infectología Institucional SRL, Buenos Aires University, Buenos Aires, Argentina.
54. Department of Surgery, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom.
55. Department of Surgery, Numune Training and Research Hospital, Adana, Turkey.
56. Department of Surgery, University Clinical Center of Tuzla, Tuzla, Bosnia and Herzegovina.
57. Department General Surgery, Kipshidze Central University Hospital, Tbilisi, Georgia.
58. Department of Digestive Surgery, Cannes Hospital, Cannes, France.
59. Department of Surgery, School of Medicine, Pontificia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil.
60. Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium.
61. School of Pharmacy, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Eric Williams Medical Sciences Complex, Uriah Butler Highway, Champ Fleurs, Trinidad and Tobago.

63. Division of Acute Care Surgery, Program in Trauma, R Adams Cowley Shock Trauma Center, University of Maryland, Baltimore, Maryland, United States of America.
64. Department of Surgical Sciences, Cannizzaro Hospital, University of Catania, Catania, Italy.
65. General Surgery, Versilia Hospital, Usl Nordovest, Tuscany, Italy
66. Department of Surgery, Maggiore Hospital, Bologna, Italy.
67. Department of Surgery, University Hospital of Trauma, Tirana, Albania.
68. School of Pharmacy, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia.
69. Department of Microbiology, Bicêtre Hospital, Paris-Sud University, La Kremlin-Bicêtre, France.
70. Department of Surgery, John Peter Smith Health Network, Fort Worth, Texas, United States of America.
71. Département d'Anesthésie-Réanimation, CHU Amiens-Picardie, and INSERM U1088, Université de Picardie Jules Verne, Amiens, France.
72. Department of Surgery, Pirogov Russian National Research Medical University, Moscow, Russian Federation.
73. Department of Emergency Medicine, Mediclinic Middle East, Al Ain Hospital, Al-Ain, United Arab Emirates.
74. Sudan National Public Health Laboratory, Federal Ministry of Health, Khartoum, Sudan.
75. Department of Medicine, Infectious Disease Division, King Fahad Medical City, Riyadh, Saudi Arabia.
76. Escuela de Medicina, Facultad de Salud, Universidad del Valle, Cali, Colombia.
77. Department of General Surgery, Trauma and Emergency Surgery Division, ABC Medical School, Santo André, SP Brazil.
78. Department of Surgery, Virginia Commonwealth University, Richmond, Virginia, United States of America.
79. Department of Surgery, Pesaro Hospital, Pesaro, Italy
80. Department of Surgery, Clínica Foianini, Santa Cruz, Bolivia.
81. Division of Trauma Surgery, Department of Surgery, School of Medical Sciences, University of Campinas (Unicamp), Campinas, SP Brazil.
82. Istituto Clinico San Rocco di Franciacorta, Brescia, Italy.
83. Department of Surgery, Bharati Vidyapeeth Deemed University Medical College and Hospital, Sangli, Maharashtra, India.
84. Infectious Diseases Department, "C. Poma" Hospital, Mantova, Italy.
85. 6th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece.
86. Department of General Surgery, Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt.
87. Second Department of Surgery, Aretaieion University Hospital, National and Kapodistrian University of Athens, Athens, Greece.
88. Intensive Care Unit, Modena University Hospital, Modena, Italy.
89. The Ohio State University Wexner Medical Center, Columbus, Ohio, United States of America.
90. Department of Surgery, Hospital Universitário Terezinha de Jesus, Faculdade de Ciências Médicas e da Saúde de Juiz de Fora, Juiz de Fora, Brazil.
91. Center for Global Health, Mito Kyodo General Hospital, University of Tsukuba, Mito, Ibaraki Japan.
92. Peruvian Navy Medical Center, Lima, Peru.
93. Unit of Endocrine, Head, and Neck Surgery and Unit of Surgical Infections Support, Department of General Surgery, Parc Taulí, Hospital Universitari, Sabadell, Spain.
94. Hospital Privado Centro Médico de Caracas and Hospital Vargas de Caracas, Caracas, Venezuela.
95. Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kuala Lumpur, Malaysia.
96. Department of General and Thoracic Surgery, University Hospital Giessen, Giessen, Germany.
97. MEDILAB Dr Mustafa Dr Richter OG, Academic Teaching Laboratories, Clinical Microbiology and Infection Control, Paracelsus Medical University, Salzburg, Austria.
98. Department of Surgery, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany.
99. Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America.
100. Department of Visceral, Transplant and Thoracic Surgery, Innsbruck Medical University, Innsbruck, Austria.
101. Department of Surgery, University of Texas Health Science Center at Houston, Houston, Texas, United States of America.
102. Division of Infectious Diseases, Department of Internal Medicine American University of Beirut, Beirut, Lebanon.
103. Department of Surgery Philadelphia VA Medical Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America.
104. Department of Microbiology, Gandhi Medical College, Bhopal, India.
105. Clinic for Emergency Surgery, Medical Faculty University of Belgrade, Belgrade, Serbia.
106. Department of Surgery, Assia Medical Group, Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel.
107. Third Department of General Surgery, Jagiellonian University Medical College, Krakow, Poland.
108. Department of Internal Medicine, Royal Hospital, Muscat, Oman.
109. Department of Emergency Surgery, City Hospital, Mozyr, Belarus.
110. Department of Pharmacology and Therapeutics, College of Health Sciences, Makerere University, Kampala, Uganda.
111. General, Acute Care, Abdominal Wall Reconstruction, and Trauma Surgery, Foothills Medical Centre, Calgary, Alberta, Canada.
112. Department of Gastrointestinal Surgery, Stavanger University Hospital, Stavanger, Norway.
113. Department of Primary Care and Emergency Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan.
114. Department of Surgery, The Brunei Cancer Centre, Jerudong Park, Brunei.
115. Department of Microbiology, Virology and Immunology, Kharkiv National Medical University, Kharkiv, Ukraine.
116. Department of Surgery, Edendale Hospital, Pietermaritzburg, South Africa.
117. Division of Acute Care Surgery and Surgical Critical Care, Department of Surgery, Los Angeles County and University of Southern California Medical Center, University of Southern California, Los Angeles, California, United States of America.
118. Fourth Surgical Department, General Hospital G. Papanikolaou, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece.
119. Department of General Surgery, Erzincan University, Faculty of Medicine, Erzincan, Turkey.
120. Department of Pharmacy, Lebanese, International University, Beirut, Lebanon.
121. School of Life Sciences and the ithree Institute, University of Technology, Sydney, New South Wales, Australia.
122. Department of Biomedical Sciences and Public Health, Unit of Hygiene, Preventive Medicine and Public Health, UNIVPM, Ancona, Italy.
123. University Hospitals of Leuven, Clinical Department of Laboratory Medicine, Leuven, Belgium; KU Leuven, Department of Microbiology and Immunology, Leuven, Belgium.
124. Hospital Central Dr Ignacio Morones Prieto, San Luis Potosi, Mexico.
125. Department of Surgery, Division of Trauma, University of Arizona, Tucson, Arizona, United States of America.
126. Department of Surgery, York Teaching Hospital NHS Foundation Trust, York, United Kingdom.
127. Center for Disease Dynamics, Economics and Policy, Washington, District of Columbia, United States of America.
128. Department of Surgery, Yonsei University College of Medicine, Seoul, South Korea.
129. Department of Anaesthesiology and Critical Care, Hôpital Nord, Assistance Publique-Hôpitaux de Marseille, Aix Marseille Université, Marseille, France.
130. Abdominal Center, University Hospital Meilahti, Helsinki, Finland.
131. Department of Surgery, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.
132. Division of Infectious Diseases, Division of Emergency Medicine, Washington University School of Medicine, St. Louis, Missouri, United States of America.
133. Department of Surgery, Liao KH Consulting, Mt Elizabeth Novena Hospital, Singapore & Yong Loo Lin School of Medicine, National University of Singapore.
134. Surgical Disciplines, Immanuel Kant Baltic Federal University/Regional Clinical Hospital, Kaliningrad, Russian Federation.
135. Division of Infectious Diseases, Department of Clinical Pathology, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.
136. Clinical Microbiology and Infectious Diseases, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Vermaak &

Partners/Pathcare Pathologists; Wits Donald Gordon Medical Centre, Johannesburg, South Africa.

137. Department of Surgery, Universidad Nacional de Asuncion, Asuncion, Paraguay.

138. Department of Surgery, University of Washington, Seattle, Washington, United States of America.

139. Clinical Research Center, Fundacion Valle del Lili, Cali, Colombia.

140. First Department of Surgery, Tzaneion General Hospital, Piraeus, Greece.

141. Department of Surgery Università Politecnica delle Marche, Ancona, Italy.

142. Multidisciplinary Intensive Care Research Organization (MICRO), Wellcome Trust-HRB Clinical Research, Department of Clinical Medicine, Trinity Centre for Health Sciences, St James' University Hospital, Dublin, Ireland.

143. Department of Surgery, Post-Graduate Institute of Medical Sciences, Rohtak, India.

144. Servicio de Anestesia y Reanimación, Hospital Universitario La Paz Madrid, Madrid, Spain.

145. Department of Surgery, Radiology, University Hospital of the West Indies, Kingston, Jamaica.

146. General Surgery Department, Centro Hospitalar de São João, Porto, Portugal.

147. Anesthesiology and Intensive Care, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy.

148. Infectious Diseases Division, Department of Medicine, Prince Mohamed Bin Abdulaziz Hospital, Ministry of Health, Riyadh, Saudi Arabia.

149. Departments of Medicine, Clinical Epidemiology and Biostatistics, and Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada.

150. Second Surgical Clinic, Emergency Hospital of Craiova, Craiova, Romania.

151. Infectious Disease Unit, University Hospital of Pisa, Italy.

152. Department of Microbiology, Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal.

153. Department of Surgery, University of Colorado, Denver Health Medical Center, Denver, Colorado, United States of America.

154. Department of Surgery, Division of Acute Care Surgery, and Center for Sepsis and Critical Illness Research, University of Florida College of Medicine, Gainesville, Florida, United States of America.

155. Department of Surgery, University of KwaZulu-Natal, Durban, South Africa.

156. Department of Surgery, University of Michigan, Ann Arbor, Michigan, United States of America.

157. Department of Surgery, Emergency Hospital of Bucharest, Bucharest, Romania.

158. Center of Anti-Infective Research and Development, Hartford, Connecticut, United States of America.

159. Department of General Surgery, Lewisham & Greenwich NHS Trust, London, UK.

160. Department of Laboratory Medicine, Division of Clinical Microbiology, Karolinska University Hospital Huddinge, Stockholm, Sweden.

161. Research Unit, Health Policy Consult, Weija, Accra, Ghana.

162. Department of Surgery, University of Ilorin, Teaching Hospital, Ilorin, Nigeria.

163. Department of Surgery, King Abdullah University Hospital, Irbid, Jordan.

164. Department of Surgery and Critical Care, Universidad del Valle, Fundación Valle del Lili, Cali, Colombia.

165. Department of Surgery, Hassan II University Hospital, Medical School of Fez, Sidi Mohamed Benabdellah University, Fez, Morocco.

166. Bacteriology and Virology Department, Centre Hospitalier Universitaire Sourou Sanou, Bobo Dioulasso, Burkina Faso.

167. Infectious Diseases Unit, Bolzano Central Hospital, Bolzano, Italy.

168. Intensive Care Medicine Department, Centro Hospitalar São João, University of Porto, Porto, Portugal.

169. Department of Surgery, Santa Casa de Sao Paulo School of Medical Sciences, São Paulo, Brazil.

170. Department of Surgery, Sant'Antonio Abate Hospital, Gallarate, Italy.

171. Surgery I Unit, Centro Hospitalar Tondela Viseu, Viseu, Portugal.

172. Unit of Prevention and Infection Control, Center of Hospital Epidemiology, São João Hospital Centre, Porto, Portugal.

173. National Institute for Infectious Diseases—INMI—Lazzaro Spallanzani IRCCS, Rome, Italy.

174. Department of Anesthesia and Intensive Care, Azienda Ospedaliero-Universitaria Parma, Parma, Italy.

175. Department of Surgery, UMC Ljubljana, Ljubljana, Slovenia.

176. Laboratory of Clinical Microbiology, Department of Infectious Diseases, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

177. Hamilton Health Sciences, Hamilton, ON, Canada London Health Sciences, London, Ontario, Canada.

178. Fourth Department of Internal Medicine and Infectious Diseases Unit, National and Kapodistrian University-Medical School, Attikon University General Hospital, Athens, Greece.

179. John Farman Intensive Care Unit, University Hospitals, NHS Foundation Trust, Cambridge, United Kingdom.

180. Instituto Nacional del Cáncer Rosa Tavares (INCART), Profesor-Investigador, Universidad Autónoma de Santo Domingo (UASD), Dominican Republic.

181. Department of General and Emergency Surgery, Riga East University Hospital 'Gailezers', Riga, Latvia.

182. Department of Trauma, Hospital Santo Tomas, Panama City, Panama.

183. National Institute for Health Research, Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, Hammersmith Campus, London, United Kingdom.

184. Department for Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Thüringen, Germany.

185. Department of General Surgery, Jesenice General Hospital, Jesenice, Slovenia.

186. Department of Clinical Research & Innovation in Pneumonia and Sepsis, Vall d'Hebron Institute of Research (VHIR), Barcelona, Spain.

187. Trauma and Acute Care Service, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

188. Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia.

189. General Surgery Department, Colorectal Surgery Unit, La Paz University Hospital, Madrid, Spain.

190. Service of Bacteriology, Paris Diderot Sorbonne University, Bichat-Claude Bernard University Hospital, HUPNSV, Paris, France.

191. General Surgery Department, Medical University, University Hospital St George, Plovdiv, Bulgaria.

192. General Surgery Department, Military teaching hospital, Dakar, Senegal

193. Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

194. JPS Health Network, Texas, United States of America.

195. Department of Aeromedical Services for Emergency and Trauma Care, Ehime University Graduate School of Medicine, Ehime, Japan.

196. Department of Surgery, Western Michigan University School of Medicine, Kalamazoo, Michigan, United States of America.

197. Trauma Surgery Department, University of Maryland School of Medicine, Baltimore, Maryland, United States of America.

198. Clinical Epidemiology Unit, IRCCS Policlinico San Matteo Foundation, Pavia, Italy.

199. Department of Surgery, Catholic University of Sacred Heart, Policlinico A Gemelli, Rome, Italy.

200. Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

201. Department of Surgery Patan Hospital, Patan Academy of Health sciences, Lalitpur, Kathmandu, Nepal

202. Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy.

203. Department of Health Sciences, Faculty of Science, University of Mauritius, Réduit, Mauritius.

204. School of Medicine, European University Cyprus, Nicosia, Cyprus.

205. Office of Hospital Epidemiology/Infection Prevention and Control, University of Virginia Health System, Charlottesville, Virginia, United States of America.

206. Department of Surgery, Faculty of Medicine, Thammasat University Hospital, Thammasat University, Pathum Thani, Thailand.

207. General Surgery Department, Letterkenny Hospital, Letterkenny, Ireland.

208. Department of Surgery, North Estonia Medical Center, Tallinn, Estonia.

209. Intensive Care Unit, Centre Hospitalier Saint Joseph-Saint Luc, Lyon, France.

210. Department of Emergency Surgery. Parma Maggiore Hospital, Parma, Italy.

211. First Division of Infectious Diseases, Cotugno Hospital, Azienda Ospedaliera dei Colli, Naples, Italy.

212. Surgery Health Care Group, Hull and East Yorkshire Hospitals NHS Trust, Hull, United Kingdom.

213. PHP medical and infectious diseases ICU, Bichat Hospital, Paris, France.

214. Institute of Infectious Diseases, Catholic University, Rome, Italy.

215. Department of Molecular Biology, Tran Hung Dao Hospital, Hanoi, Vietnam.

216. First Department of Surgery, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic.

217. Department of Surgery, Medical University of Graz, Graz, Austria.

218. Trauma, Emergency Surgery, and Surgical Critical Care, Massachusetts General Hospital, Boston, Massachusetts, United States of America.

219. Department of Surgery, Medical School University of Pécs, Pécs, Hungary.

220. Infectious Diseases Unit, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy.

221. Instituto de Salud Global, ISGlobal - Hospital Clinic, Universitat de Barcelona, Barcelona, Spain.

222. Infectious Diseases Unit, Ospedale Policlinico San Martino—IRCCS per l'Oncologia, University of Genoa (DISSAL), Genoa, Italy.

223. Department of Urology, Pediatric Urology and Andrology, Medical Faculty of the Justus Liebig University Giessen, Giessen, Germany.

224. Department of Emergency Medicine and Neurosurgery, Stony Brook University School of Medicine, Stony Brook, New York, United States of America.

225. State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University, Zhejiang, China.

226. Trauma and Emergency Surgery Department, Chang Gung Memorial Hospital, Taoyuan City, Taiwan.

227. Department of Surgery, MOSC Medical College Kolenchery, Cochin, India.

228. Infection Control Unit, Angers University, CHU d'Angers, Angers, France.

Address correspondence to:

Dr. Massimo Sartelli

Department of Surgery

Macerata Hospital

Macerata, Italy

E-mail: massimosartelli@gmail.com