AGAR Paediatric Data Analysis Plan

Investigators: Chris Blyth; Anita Williams; Anita Campbell; Denise Daley; Jan Bell; Geoff Coombs; Alison Kesson; Pheobe Williams; Brendan McMullen; Adam Irwin; Morgyn Warner; Louise Cooley

Contents

Acronyms 1

1. Aim and Objectives 2
2. Background 2
3. Study Design and Population 3
4. Variables 3
5. Statistical Methodology 4
   - 5.1. General Methodology 4
   - 5.2. Primary Data Analysis 4
   - 5.3. Secondary Data Analysis 4
6. Outputs 4

References 5

Acronyms

Acronym	Full Text
ABS	Australian Bureau of Statistics
AGAR	Australian Group on Antimicrobial Resistance
AMR	Antimicrobial Resistance
ASA	Australian Society for Antimicrobials
ASSOP	Australian *S. aureus* Sepsis Outcome Programme
EnSOP	*Enterobacteriaceae* Sepsis Outcome Programme
ESBL	Extended spectrum β-lactamase producing
GnSOP	Gram-negative Sepsis Outcome Program
ICU	Intensive Care Unit
LOS	Length of stay
MDR	Multi-drug resistance
MRSA	Methicillin-resistant *S. aureus*
PRC	Principal referral centres
VRE	Vancomycin-resistant *Enterococcus*
WSPID	World Society for Paediatric Infectious Diseases

1. Aim and Objectives

The aim of this analysis is to describe the microbiological and clinical characteristics of paediatric patients and investigate any differences between the paediatric and adult populations with bacteraemia in Australia whose data has been collected in AGAR between 2013 and 2021.

The objectives are

- Describe the microbiological and clinical characteristics of paediatric patients with bacteraemia whose data has been collected in AGAR in 2021
- Examine and describe trends in the microbiological data over time stratified by age and location, including detailed antibiotic susceptibility patterns of patients with a MDR organism infection, including (but not limited to) Methicillin-Resistant *Staphylococcus aureus* (MRSA), Expended-Spectrum Beta-Lactamase (ESBL) positive and Carbapenem Resistant Gram-negative infections
- Explore and compare the differences between the adult and paediatric populations for causative pathogens and resistance profiles within AGAR over time

2. Background

The Australian Group on Antimicrobial Resistance (AGAR), founded in 1986, has grown over time to achieve targeted surveillance for *Staphylococcus aureus*, *Enterococcus* species and Gram-negative bacteraemia across all Australian states and territories. As of 2020, 30 laboratories servicing 49 institutions from all Australian states and mainland territories were reporting data to AGAR (1–3).

AGAR commenced surveillance of the key gram-negative pathogens, *Escherichia coli* and *Klebsiella* species, in 1992. Surveys were conducted biennially until 2008 when annual surveys commenced, alternating between community- and hospital-onset infections. In 2004, Enterobacter species was added. In 2013, AGAR commenced the Australian *S. aureus* Sepsis Outcome Programme (ASSOP) and the *Enterobacteriaceae* Sepsis Outcome Programme (EnSOP) which focused on the collection of resistance and some demographic data on all isolates prospectively from patients with bacteraemia. In 2015, *Pseudomonas aeruginosa* and *Acinetobacter* species were added, with the program now referred to as the Gram-negative Sepsis Outcome Program (GnSOP) (1–3).

The AGAR reports feed into the key pillar objective #5 “Integrated Surveillance and Response to Resistance and Usage” of the National Antimicrobial Resistance Strategy of Australia(4). The AGAR reports allow healthcare professionals and policy makers to “use evidence-based surveillance and monitoring data to inform actions and responses to contain antimicrobial resistance” [page 11](4).

Currently, annual reports of the whole population of AGAR are produced, however previous analysis of the AGAR data comparing adult (>18 years) and paediatric (≤18 years) suggests there are lower rates of resistant organisms isolated in children, with different phenotypes and lower mortality rates. In 2018, the World Society for Paediatric Infectious Diseases (WSPID) recently declared that surveillance programs should present neonatal- and paediatric-specific data to assist with strengthening knowledge (5). Furthermore, various reports from Australia and Europe suggest there are differences in the burden of various organisms, not only between adults and children, but within different age groups of children. For example, Gram-negative MDR organisms were previously found to disproportionately burden children, with higher odds of death in children with an ESBL-bacteraemia vs non-ESBL bacteraemia when compared to the same ratio in adults (6). In a European study, isolated from children <1 year had less

resistance than those isolated from children >1 year old (7). In a Scottish study, bacteraemia in children <1 year are more likely to be healthcare associated, whilst children aged 1-15 years are more often likely community associated (8). These findings impact the empiric treatment guidelines and stewardship initiatives and highlights the value of paediatric-specific reporting of bacteraemia.

AGAR Methodology

The AGAR surveillance system captures clinical and microbiological data from unique patient episodes of bacteraemia. In patients with more than one isolate, a new episode is defined as a new positive blood culture more than two weeks after the initial positive culture. An episode is defined as community onset if the first positive blood culture is collected 48 hours or less after admission, and as hospital onset if collected more than 48 hours after admission.

Data collected from the laboratory for each episode includes the patients date of birth, sex, postcode of residence, date of sample collected, the organism isolated (genus and species), and the antimicrobial susceptibility test results (minimum inhibitory concentrations). If the patient is admitted to hospital, the dates of admission and discharge are recorded. Depending on the level of participation by the healthcare facility, limited clinical and outcome data are also provided. These included the principal clinical manifestation, and the outcome (died, all-cause or survived) at seven and 30 days.

Identification of the organism is undertaken using standard laboratory methods. In recent surveys, this is predominantly by matrix-assisted laser desorption ionization (MALDI) using either the Vitek MS® (bioMérieux, France) or the MALDI Biotyper (Bruker Daltonics, Germany. Participating laboratories performed antimicrobial susceptibility testing using the Vitek2® (bioMérieux, France) or BD Phoenix™ (Becton Dickinson, USA) automated microbiology systems according to the manufacturer's instructions.

Additional specific methodological details relating to organism specific testing and molecular typing are outlined in the relevant AGAR reports (1–3).

3. Study Design and Population

This is a retrospective data analysis of routine microbiological and clinical data reported for surveillance purposes. The data is pseudonymised, in that there is a patient ID (most frequently blood culture laboratory number) which could link back to the individual at the hospital from which the data was reported.

The population will be divided into two groups – paediatric (≤16 years) and adult (>16 years). Further division of the age groups of the paediatric population include 0-28 days, 29-90 days, 4-11 months, 12-59 months, and 5 -16 years.

To account for changes over time within the population, clinical and microbiological methodologies, trends will be assessed in three-year time periods (2013-2015; 2016-2018; 2019-2021).

4. Variables

Population variables include demographics (age, sex, location) principal clinical manifestation, and outcomes (LOS, 7- and 30-day all-cause mortality)

Microbiological include genus, species, susceptibility results, species specific results (e.g., inducible clindamycin for *S. aureus*) genotype, and onset-type.

5. Statistical Methodology

5.1. General Methodology

Descriptive statistics for description of population and isolates for the overall population and per year, stratified by age, sex and jurisdiction where appropriate. Categorical data will be assessed using chi-squares or Fisher's exact test. Continuous data will be assess using Student t tests or Mann-Whitney U test.

Initial cleaning will be performed in Microsoft Excel, with analysis performed using R and the R for AMR package.

5.2. Primary Data Analysis

Prevalence of resistance to various antibacterial agents will be reported overall and by bacterial species and presented as proportions of susceptible (S), intermediate (I) or resistant (R) [as is clinically relevant]. Prevalence of WHO priority pathogens over time will be described (9).

The definitions used by Magiorakos *et al.*(10) will be applied, where multidrug resistance (MDR) is defined as resistance to one or more agents in three or more antimicrobial categories. For each species, antimicrobials were excluded from the count if affected by natural resistance mechanisms. Key MDRs include MRSA, VRE and carbapenem-resistant *Enterobacterales*.

Where appropriate, rates over time will be calculated and statistical significance will be evaluated using chi-square and Fisher exact testing (depending on sample size) and will utilise a two tailed *p*-value <0.05.

Annual cumulative population incidence rates will be calculated using Australian Bureau of Statistics (ABS) census population estimates for ≤16 and >16 years, considering the proportion of paediatric and adult principal referral centres (PRCs) captured through AGAR, along with the number of bacteraemia presentations captured for key pathogens over the surveillance period.

5.3. Secondary Data Analysis

Binary multivariable logistic regression will be used to evaluate the potential association between bacteraemia and risk factors. Comparison and analysis of risk difference between paediatric and adult populations will be performed, with potentially significant covariates considered *a priori* and those with a *p*-value < 0.1 on univariate analysis will be included in a multivariable regression model.

6. Outputs

The results of this analysis will be written up into three reports

1. The 2021 Paediatric AGAR report
2. Paediatric Bacteraemia in Australia: An Analysis of AGAR surveillance data 2013-2021
3. An updated analysis of Campbell et. al., (2020) expanding the years of data included in the analysis.

These reports will be made publicly available, including discussions with relevant stakeholders (AGAR, etc). An abstract will be submitted to the Australian Society for Antimicrobials (ASA) 2023 conference.

References

1. Bell JM, Lubian AF, Partridge SR, Gottlieb T, Iredell J, Daley DA, et al. Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GnSOP) Annual Report 2020. Commun Dis Intell [Internet]. 2022 [cited 2022 Oct 13];45. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/2A15CD097063EF40CA2587CE008354F1/$File/australian_group_on_antimicrobial_resistance_agar_australian_gram_negative_sepsis_outcome_programme_gnsop_annual_report_2020.pdf

2. Coombs GW, Daley DA, Yee NW, Shoby P, Mowlaboccus S. Australian Group on Antimicrobial Resistance (AGAR) Australian Staphylococcus aureus Sepsis Outcome Programme (ASSOP) Annual Report 2020. Commun Dis Intell [Internet]. 2022 Apr 26 [cited 2022 Oct 13];46. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/2A15CD097063EF40CA2587CE008354F1/$File/australian_group_on_antimicrobial_resistance_agar_australian_staphylococcus_aureus_sepsis_outcome_programme_assop_annual_report_2020.pdf

3. Coombs GW, Bell JM, Daley D, Collignon P, Cooley L, Gottlieb T, et al. Australian Group on Antimicrobial Resistance Sepsis Outcomes Programs: 2020 Report [Internet]. Sydney, Australia: ACSQHC; 2021. Available from: http://agargroup.org.au/download/15994/

4. Department of Health. Australia's National Antimicrobial Resistance Strategy – 2020 and beyond [Internet]. Canberra, Australia: Commonwealth of Australia; 2020 Mar [cited 2022 Oct 17]. Available from: https://www.amr.gov.au/resources/australias-national-antimicrobial-resistance-strategy-2020-and-beyond

5. Buttery J, Yang Y, Sharland M, World Society for Pediatric Infectious D. World Society for Pediatric Infectious Diseases declaration on combating antimicrobial resistance in children. World J Pediatr. 2018/10/07 ed. 2018 Dec;14(6):523–4.

6. Campbell AJ, Daley DA, Bell JM, Pang S, Coombs GW, Carapetis JR, et al. Progress towards a coordinated, national paediatric antimicrobial resistance surveillance programme: Staphylococcus aureus, enterococcal and Gram-negative bacteraemia in Australia. J Antimicrob Chemother. 2020/03/11 ed. 2020 Jun 1;75(6):1639–44.

7. Bielicki JA, Lundin R, Sharland M, Project A. Antibiotic Resistance Prevalence in Routine Bloodstream Isolates from Children's Hospitals Varies Substantially from Adult Surveillance Data in Europe. Pediatr Infect J. 2015/01/22 ed. 2015 Jul;34(7):734–41.

8. Murdoch F, Danial J, Morris AK, Czarniak E, Bishop JL, Glass E, et al. The Scottish enhanced Staphylococcus aureus bacteraemia surveillance programme: the first 18 months of data in children. J Hosp Infect. 2017 Oct;97(2):127–32.

9. WHO. Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics [Internet]. [cited 2021 Feb 24]. Available from: https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1

10. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012 Mar 1;18(3):268–81.