TARGET PRODUCT PROFILE FOR THERAPY OF NEONATAL SEPSIS IN HIGH RESISTANCE SETTINGS

World Health Organization

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Introduction

Disease burden

Neonatal sepsis is a systemic infection occurring in infants ≤ 28 days old which accounts for 15% of deaths in neonates globally.[1,2] The highest burden of neonatal sepsis is in South Asia and sub-Saharan Africa,[3] although it is recognized that there may be some overdiagnosis due to the low specificity of clinical diagnosis. The aetiology of neonatal sepsis is largely unknown in low- and middle-income countries (LMICs), as surveillance data are sparse due to low rates of microbiological diagnostics being performed to confirm suspected neonatal sepsis and low detection rates of bacterial pathogens due to a very low number of positive blood cultures.[4,5,6]

The epidemiology of pathogens differs regionally and depends on time of onset of infection, but involves Gram-negative pathogens (mainly *Escherichia coli* and *Klebsiella* species, but also *Acinetobacter* species and *Pseudomonas aeruginosa*), *Staphylococcus aureus* and other Gram-positive cocci.[7]

Antibiotic resistance

Resistance rates are extremely variable, and only a few studies with adequate data exist. Nevertheless, multidrug-resistant (MDR) pathogens, resistant to more than one agent in three or more antibiotic categories, are estimated to account for approximately 30% of all global neonatal sepsis mortality.[8]

Available treatment options

Few antibiotics have been tested and licensed for either the empirical treatment of clinically diagnosed neonatal sepsis or for cases suspected or confirmed to be caused by MDR bacteria. The World Health Organization (WHO) recommended treatment of ampicillin or penicillin in combination with gentamicin may not be adequate in many places due to a global increase in resistance in Gram-negative pathogens.

Therapies in development

Regulatory requirements and incentives exist for paediatric studies with new drugs, but economic incentives are lacking for the development of new antibiotics overall. No registrational studies are under way for new antibiotic treatments for neonatal sepsis, and consequently public health studies are required with appropriate funding to fill this gap. Recently approved new antibiotics for use in adults (i.e. ceftazidime-avibactam, meropenem-vaborbactam) may potentially be suitable, and their use could be explored for neonatal infections. Development activities would be supported by an agreed target product profile (TPP) tailored to prioritize treatment in settings with a high prevalence of resistance.

Purpose of the TPP

A TPP developed by the Global Antibiotic Research and Development Partnership (GARDP) with World Health Organization (WHO) involvement, primarily focusing on empirical treatment of neonatal sepsis, already exists.[9] This process would build on that work following the new more inclusive WHO standard procedure for developing TPPs. Due to the incomplete knowledge around the wide variety of aetiology and resistance rates in different regions, and thus the types of target products and treatments required, this TPP addresses the known challenge of specific therapy for infections caused by different MDR and extensively drug resistant (XDR) organisms (resistant to all but one or two antibiotic categories), including carbapenem-resistant organisms. The expert meeting recommended postponing the TPP for empirical therapy of neonatal sepsis until more reliable data from ongoing epidemiological studies is available. Furthermore, the meeting recommended changing the title of the second TPP to TTP for therapy in children including neonates with MDR Gram-negative infections, to recognize the requirement of such a TPP to cover all XDR/MDR infections across age groups and to secure sufficient study subjects by not limiting the inclusion criteria to neonates only. Antibiotic research efforts should go hand in hand with the development of corresponding rapid diagnostics that are inexpensive and that identify the pathogen as well as the susceptibility profile.

Access and affordability

- Access to new essential antibacterial treatments is an essential part of universal health coverage. Developers should commit to an access and stewardship strategy that promotes availability at fair prices. A fair price is one that is affordable for health systems and patients, but at the same time provides sufficient market incentive for industry to invest in innovation and the production of quality essential health products.[10] To ensure access to patients in many countries, developers are invited to collaborate with WHO, GARDP and the Medicines Patent Pool where appropriate.
- Governments need to commit to ensure availability and affordability of essential new antibiotic treatments. In particular for reserve antibiotics,[11] governments should explore models where procurement and reimbursement are linked to availability instead of volume to foster appropriate use.
- Stewardship and appropriate use are essential to preserve the effectiveness of any new antibacterial treatment. Developers should not register the product for use in animals or plants or develop a treatment of the same class for use in animals or plants. The above-mentioned access and stewardship plan should be based on ethical promotion and distribution. Manufacturing should be in line with best industry practices in the management of emissions to the environment to minimize the risks of spreading antimicrobial resistance (AMR).

TPP for therapy in children including neonates with MDR Gram-negative infections

	Minimal TPP	Preferred TPP
Indication for use	Serious bacterial infections in environments with high prevalence of XDR Gram-negative bacteria for which there are limited or no treatment options.	All the criteria included in the minimal TPP, and neonatal sepsis/meningitis caused by MDR and XDR Gram-negative pathogens, including *K. pneumoniae* and *Acinetobacter* spp., failing on optimal current treatment.
Target population	Hospitalized children with an emphasis on neonates with severe infections and failure on current treatment.	Hospitalized children including neonates with severe infections, failure on current treatment and a very high likelihood of being caused by MDR/XDR Gram-negative pathogens.
Access and affordability	See Introduction and paragraph on Access and affordability.	See Introduction and paragraph on Access and affordability.
Safety/tolerability	The need for safety and tolerability data from animal juvenile toxicity models should be considered on a case-by-case basis.	The need for safety and tolerability data from animal juvenile toxicity models should be considered on a case-by-case basis. No requirement to routinely monitor drug levels.
In vitro activity	MDR and XDR Gram-negative pathogens, including *K. pneumoniae* and/or *Acinetobacter* spp., activity tested in bacteria with defined resistance mechanisms (especially β-lactams, aminoglycosides, fosfomycin). Low cross-resistance to currently used antibiotics, and low propensity for resistance development.	MDR and XDR Gram-negative pathogens, including *K. pneumoniae* and *Acinetobacter* spp., activity tested in bacteria with defined resistance mechanisms (especially β-lactams, aminoglycosides, fosfomycin) and clinical strains, especially carbapenem-resistant strains, no cross-resistance to currently used antibiotics. Low propensity for resistance development.
Clinical efficacy	Proven efficacy in adults, and showing safety and refining the pharmacokinetics (PK) in neonates and children. Demonstrate clinical efficacy in adults with confirmed XDR infections.	Proven efficacy in adults, and showing safety and refining the PK in neonates and children. Demonstrate clinical efficacy in adults with confirmed XDR infections.
Formulation/ presentation	Injectable and oral formulations	Injectable and oral formulations
Dose regimen	1–4x daily, treatment duration depending on initial clinical response to treatment and clinical focus on site of infections.	1–4x daily, treatment duration depending on initial clinical response to treatment and clinical focus on site of infections.
Route of administration	Intravenous injection or infusion	Intravenous injection or infusion and oral (step down)
Product stability and storage	Heat-stable, 3-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity).	Heat-stable, 3-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity).
Pharmacokinetics	PK data available to support use in all age groups, including neonates, derived from population PK modelling in neonates and across all age groups.	PK data available to support use in all age groups, including neonates, population PK modelling in neonates and across all age groups, population PK modelling to support activity in cerebrospinal fluid.
Drug interactions	Minimal drug-drug interactions (DDIs) with common intensive care unit (ICU) drugs. For HIV, tuberculosis (TB) and malaria medication, DDIs should be studied if relevant, in addition to those that have already been studied.	No DDIs with common ICU drugs. For HIV, TB and malaria medication, DDIs should be studied if relevant, in addition to those that have already been studied.

WHO documents

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