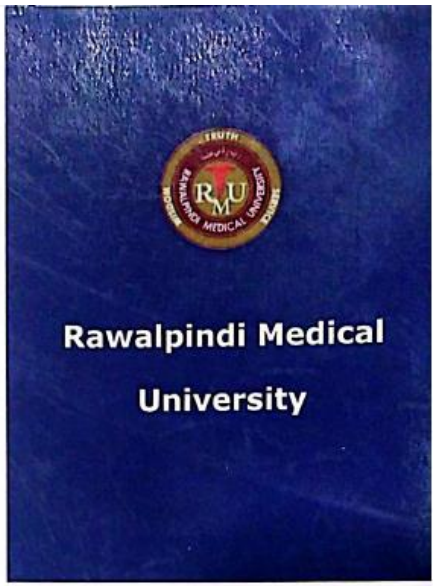
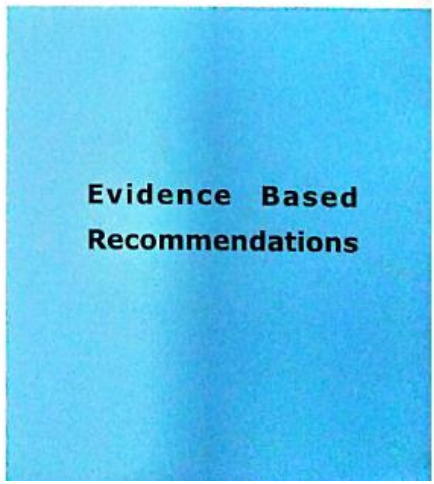
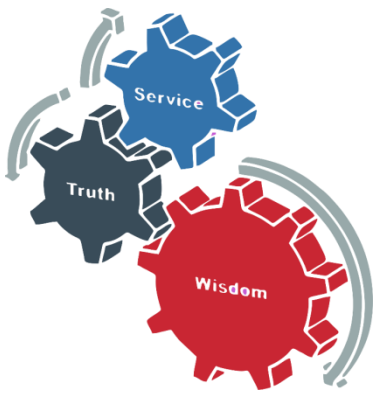


RMU Salmonella Infection Treatment Guidelines



Motto



Vision

- To Impart Evidence Based Research Oriented Medical Education.
- To Provide Best Possible Patient Care.
- To Inculcate the Values of Mutual Respect & Ethical Practice of Medicine.

These are Evidence based empirical recommendations for antimicrobial usage in Salmonella infections of Rawalpindi Medical University and Allied Hospitals. Evidence is based on the available data of 2019 of antimicrobial resistance patterns seen in blood cultures.

Treatment should be reviewed clinically at 48-72 hours with the results of clinical findings, imaging results, microbiological cultures and other laboratory findings. Antimicrobials can then be stopped, switched to oral therapy, changed to a narrow spectrum agent or continued with further review.

Expert Panel

Patron	Professor Muhammad Umar
Chair	Professor Naeem Akhtar
Convener	Dr Shireen Rafiq Dr Kiran Ahmad
Members	Prof. Rai Muhammad Asghar Prof. Seemi Gul Prof. Muhammad Khurram Dr Shireen Rafiq Dr Abrar Akbar Dr Mujeeb Khan Mrs. Nabila Shoaib Dr Kausar Izhar Dr Kiran Ahmad

Date of Issue: January 2021, Edition 1.0

Patron in Chief Message

Institutional Antimicrobial Usage Protocols is one of the most exciting initiative that Rawalpindi Medical University has taken. The threat brought on by antimicrobial resistance is a key factor driving this project.

Salmonella treatment guidelines are produced through series of discussions held between Antimicrobial Usage Policy Committee including members of various disciplines. It involved a structured and intensive discussion process to ensure that content was carefully reviewed and coordinated for consistency.

I also want to express my sincerest congratulations and heartfelt gratitude to all those involved in the preparation of this protocol, led by Professor Naeem Akhtar, for their commitment during the preparation process.

Professor Muhammad Umar
Vice Chancellor
Rawalpindi Medical University

Chairman Message

"Practice guideline would only be effective if they are adhered to"

Antimicrobial Usage Protocols emerge as an ever important intervention to support clinical decision-making through a consensual process based on evidence and collective action to tackle disease problem.

This Rawalpindi Medical University Antimicrobial Usage Protocols for Salmonella is undoubtedly one of the essential documents which will benefit all Rawalpindi Medical University and Allied hospital employees irrespective of their expertise and workplace as infections can occur to their patients at anytime and anywhere and also for judicious use of antibiotics and reducing antimicrobial resistance in hospitals. I am sure many will look forward to having this protocol.

I will like to acknowledge and thank the whole Antimicrobial Usage Policy Committee for support and patience in this long process.

Professor Naeem Akhtar
Dean Basic Sciences,
Chairman Antibiotic usage committee
Rawalpindi Medical University,
Rawalpindi.

Conveners

Dr. Shireen Rafiq

Dr. Kiran Ahmad

Members

Prof. Rai M. Asghar

Prof. Semi Gul

Prof. M. Khurram

Prof. Jahangir Sarwar

Dr. Kausar Izhar

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Acknowledgement

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Contents

1. Introduction

Prevalence of Extensively Drug Resistant Salmonella Typhi XDR Infection At RMU And Allied Hospitals

Salmonella typhi is the main specie type causing enteric fever. Enteric fever is one of the main causes of morbidity in Pakistan.

WHO used the following case definition of Typhoid fever: (WHO, 2018)

1) **Non resistant Typhoid fever**: it is defined as typhoid fever caused by Salmonella Typhi or Salmonella paratyphi A, B or C strains which are sensitive to first and second line drugs (ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, cefixime and ceftriaxone). Any isolate sensitive to first line drugs but resistant to fluoroquinolone group will also be considered as Non Resistant typhoid.

2) **Multi-drug resistant typhoid fever**: it is defined as typhoid fever caused by Salmonella Typhi or Salmonella paratyphi A, B or C strains which are resistant to the first line recommended drugs for treatment such as chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole. The strain may be sensitive or resistant to fluoroquinolone group.

3) **Extensive drug resistant typhoid fever**: it is defined by typhoid fever caused by Salmonella Typhi strain which are resistant to first line drugs, fluoroquinolones and third-generation cephalosporins (Ceftriaxone).

In 20th century typhoid fever incidence decreased due to the vaccine introduction, improved treatment, better hygiene and sanitation.

The first line treatment of Enteric fever was very successful in late 20th century with co-trimoxazole, chloramphenicol and ampicillin. Then, resistance to Chloramphenicol emerged in early period of 1970 and around 1990 multidrug resistant Salmonella typhi evolved. As a result, Fluoroquinolones came as first line antibiotic therapy for Enteric fever. (WHO, 2019)

Then quinolone resistant strains evolved. MDR and quinolone resistant strains led to the oral cefixime or parenteral ceftriaxone as the treatment of choice. (WHO, 2019)

The Provincial Disease Surveillance and Response Unit (PDSRU) reported 5274 XDR S. typhi cases from 14 districts of Sindh, from 2016 to December 2018, according to the World Health Organization (WHO). These included 76% cases form Karachi, 27% cases from Hyderabad and 4% cases from other districts of Sindh. In spite of the control measures initiated by the local government, there was a noticeable increase in reported cases from 2017 to 2018. The international surveillance for XDR S.typhi identified a case from UK and five cases from USA. Recently, another case has been reported from Canada. All these patients had a history of travel to Pakistan. (WHO, 2018)

The rationale of this study is to find out XDR cases of Enteric fever in tertiary care hospital (BBH & HFH), to treat patient at the earliest, decrease hospital stay to prevent nosocomial infections and to prevent any life threatening complications. BBH & HFH are the main tertiary care government hospitals of Rawalpindi and give treatment cover to large area.

The only gold standard test for diagnosing Enteric fever is blood cultures and stool cultures before the start of antibiotics. (WHO, 2019)

Moreover, emphasizing judicious use of antimicrobials to prevent any gross trouble that will be alarming for Pakistan as well as globally.

1. Materials and Method:

This study was conducted at Rawalpindi Medical University Allied Hospitals, on blood culture-proven Salmonella typhi cases from January 2019 to December 2019**.**

Blood cultures received in pathology lab of Allied Hospitals of Rawalpindi Medical University were incubated aerobically at 37°C. After 48 hours first subculture was done. Standard blood culture protocols were followed.

Salmonella typhi were identified as Non-lactose fermenting (NLF) colonies and gram negative rods. Standard biochemical tests including API 20E (Biomerieux) were also applied.

The samples positive for S. typhi were tested for antibiotics sensitivity on Mueller Hinton agar using modified Kirby Bauer disk diffusion method. The antibiotic disks applied were ampicillin (10µg), chloramphenicol (30µg), co-trimoxazole (1.25/23.75µg), ciprofloxacin (5µg), ceftriaxone (30µg) and azithromycin (15µg). Zones of inhibition after overnight incubation were measured according to CLSI (Clinical Laboratory Standards Institute) guidelines, 2018-2019.

Antibiotics	Sensitive	Intermediate sensitive	Resistant
Ampicilllin	≥17	14-16	≤13
Chloramphenicol	≥18	13-17	≤12
Co-trimoxazole	≥16	11-15	≤10
Ciprofloxacin	≥31	21-30	≤20
Ceftriaxone	≥23	20-22	≤19
Azithromycin	≥13	-------	≤12
Meropenem	≥23	20-22	≤19

Table 1: Antibiotic discs and zones of inhibition sizes

Antibiotic resistance pattern was noted. Those isolates which were resistant to Ampicillin, Chloramphenicol, Co-trimoxazole, Ciprofloxacin and Ceftriaxone were labelled as XDR Salmonella typhi.

2. Methodology for Formulation of Guidelines.

2.1 Panel Composition

A panel of experts was convened by Vice Chancellor Rawalpindi Medical University to formulate clinical practice guideline on ICU antimicrobial therapy.

Recommendation Panel

Patron in Chief	-	Professor Muhammad Omar
Chair		Professor Naeem Akhtar
Convener		Dr Shireen Rafiq Dr Kiran Ahmad
Members		Prof. Rai Muhammad Asghar Prof. Seemi Gul Prof. Muhammad Khurram Prof. Jahangir Sarwar Dr Abrar Akbar Dr Mujeeb Khan Mrs. Nabila Shoaib Dr Kausar Izhar Dr Fariha Sardar

2.2 Evidence Review and Formulation of Recommendations

The panel followed a process used in the development of WHO executive guidelines on typhoid management and National Antimicrobial policy of Pakistan.

The process used in the development of other guidelines that includes a systematic review of the relevant evidence and the formulation of recommendations of WHO

Specific features of the evidence base (such as risk of bias or large effect size) warranted decreasing or increasing the rating of the quality of the evidence. The strength assigned to the recommendation reflected the net benefits and net harms or trade-offs resulting from that recommendation, in addition to level of evidence available.

2.3 Data Synthesis

The evidence was synthesized using antimicrobial data from blood cultures received in pathology laboratories of RMU and Allied Hospitals.

2.4 Formulation of Recommendations

Recommendations were formulated considering the strength of the evidence available and the net benefits or net harms resulting from those treatments.

2.5 Future Revision Dates

At six monthly basis, the panel will review the antimicrobial patterns and will determine the need for guideline revisions.

2.6 Culture negative samples

Culture negative means no sign of growth/yield.

Common cause of negative cultures in suspected cases of typhoid fever

I. Previous or current administration of antityphoid antibiotics can suppress bacterial growth
II. Fastidious organisms
III. Cell dependent organisms eg Viruses
IV. Fungi
V. Major immune reactions
VI. Other causes of Fever (PUO)

3. Evidence Based Recommendations

Correct treatment begins with the correct diagnosis. Before embarking on a course of treatment, it is essential to identify the infection being treated. This includes gaining an understanding of the primary site of infection, the extent of infection around the primary site, and distant sites seeded secondarily.

The selected antimicrobial agent should have activity against identified Salmonella typhi and proven therapeutic efficacy in the infection being treated. Patient factors that may impact efficacy must be considered, including co-morbidities, concomitant therapies (drug and non-drug), patient age, and organ function.

Suggested treatments are given below. They apply to all the patients suffering from salmonella infections. When the Salmonella typhi isolated, treatment may be changed to a more appropriate antibacterial agent if necessary. If no bacterium is cultured the antibacterial can be continued or stopped on clinical grounds. Record all decisions in the notes. State the duration and indication on the drug chart. IV antibiotics that continue beyond 72 hours must have duration in the notes.

4. Principles of Treatment

1- It should be mandatory to send blood and stool culture and sensitivity samples before putting the patient on any kind of antibiotics.
2- Two sets of blood culture are optimal before starting antibiotic therapy and in those patients who are already on antibiotics but not responding to therapy.
3- Serological tests should never be relied as primary tools upon to diagnose or rule out enteric fever.
4- It is important to rule out malaria, dengue and other possible causes of febrile illness in a patient who presents with acute febrile illness of more than 3 days of duration
5- After sending baseline investigations, including blood cultures, commence empirical treatment for suspected enteric fever with either oral cefixime or IV ceftriaxone depending on the severity of the disease.
6- In the absence of a positive blood culture or if a blood culture shows no growth, re-evaluate the diagnosis and stop or modify antibiotics if not typhoid.
7- Fever defervescence is prolonged in typhoid fever and may take 5-7 days to improve. Do not rush to change antibiotics, monitor for improvement in frequency and intensity of fever.
8- The appetite and general condition of the patient may improve before improvement in fever is noticed.
9- Monitor for complications like abdominal distension, tenderness, vomiting, alteration of GCS and laboratory parameters like bicytopenia.
10- It is important to initiate antibiotic as soon as possible in severe infection or in those immune-compromised, particularly if salmonella infection is suspected.
11- This guidance should not be used in isolation; it should be supported with patient information about safety netting, back-up/delayed antibiotics, self – care, infection severity and usual duration, clinical staff education, and audits.
12- Doses need to be adjusted for age, weight and renal function.
13- Refer to drug guide for further dosing and interaction information (e.g. interaction between macrolides and statins), ALWAYS check for hypersensitivity/allergy.
14- Have a lower threshold for antibiotics in immune-compromised or in those with multiple co- morbidities; send samples for culture and seek advice.
15- Selection and use of antibiotics is based on:
Drugs in Green are first line antibiotics.
Drugs in Yellow are considered second line treatment modality.
Drugs in Red are last resort.
16- ‘Blind’ antibiotic prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis.

17- Avoid broad spectrum antibiotics (e.g. co-amoxiclav, quinolones and cephalosporins) when narrow spectrum antibiotics remain effective.

18- In pregnancy, take specimens to inform treatment. Penicillins, cephalosporins and erythromycin are not associated with increased risk of spontaneous abortion. If possible, avoid quinolones, azithromycin clarithromycin. Trimethoprim is also unlikely to cause problems unless poor dietary folate intake, or taking another folate antagonist. **If you are unsure about a particular drug's use in pregnancy contact the Pharmacist for further advice.**

4.2 Antibiotic choices for treatment of Typhoid

Antibiotic	Route	Adult dosage/day	Dosage: mg/kg/day	Duration in days
First-line antibiotics :				
Chloramphenicol	Oral, IV	500 mg QID	50 mg/kg in 4 doses*	14
Trimethoprim-Sulfamethoxazole	Oral, IV	160/800 mg BD	4-20 mg/kg: in 2 dose	14
Ampicillin/Amoxicillin	Oral, IV, IM	1000-2000 mg QID	75-100 mg/kg: in 4 doses	14
Second-line antibiotics:				
Ceftriaxone	IM, IV	1gm BD or 2 gm OD	–	10-14
Cefixime	Oral	400 mg BD	20 mg/kg: in 1-2 doses	10-14
Ciprofloxacin	Oral/IV	500 mg to 750 mg BD /400 mg BD	–	10-14
Third line antibiotics :				
Azithromycin	Oral	Patient weight <60kg: 1gm loading dose PO, then 500mg OD for 7-10 days. Patient weight > 60kg: 1 gm OD	8-10 mg/kg	7 – 10
Meropenem	IV	1 gm TID	60mg/kg/day: in 3 doses	10-14
Imipenem	IV	500mg q6hr or 1g TID	20-60mg/kg/day: in 3/4 doses	10-14
Ertapenem	IV	1 gm OD	–	10-14

** Dose of chloramphenicol may be reduced to 25 mg/kg after defervescence.*

4.3 Evidence and Recommendations

A total of 8245 blood cultures were received in RMU and Allied hospital during year 2019, out of which 911 had positive yield.

Total Blood cultures=8245

Positive growth =911 (11%)

Salmonella typhi =179 (20%)

XDR Salmonella typhi=135(75%)

Antibiotics	Total cases	Sensitive	Percentage
1.Meropenam	179	179	100
2.Azithromycin	179	162	90.4
3.Co-trimoxazole	179	74	41.2
4.Ciprofloxacin	179	71	39.6
5Ceftriaxone	179	62	34.9
6.Augmentin	179	6	3.1
7. Chloramphenicol	179	18	10

Table 2: Antibiotic sensitivity pattern of Salmonella typhi isolated from blood cultures. (CLSI 2018-19)

Evidence
Evidence: show that **Meropenem and Azithromycin** shows more than 90% activity against Salmonella typhi. (Level of Evidence: High) Activity of Co-trimoxazole, Ciprofloxacin and Ceftriaxone is less than 40% (Level of Evidence: moderate)
Recommendations
Recommendation: Azithromycin and Imipenem may be used for treatment of XDR Salmonella typhi infection as first line. (Strong Recommendation) Co-trimoxazole, Ciprofloxacin, Ceftriaxone and their combination may be used for treatment of Salmonella typhi infections as first line. (moderate Recommendation)

5. Causal Associations Between Antimicrobial Use and The Emergence of Antimicrobial Resistance

1- Changes in antimicrobial use are paralleled by changes in the prevalence of resistance.
2- Antimicrobial resistance is more prevalent in health care–associated bacterial infections, compared with those from community-acquired infections.
3- Patients with health care–associated infections caused by resistant strains are more likely than control patients to have received prior antimicrobials.
4- Areas within hospitals that have the highest rates of antimicrobial resistance also have the highest rates of antimicrobial use.
5- Increasing duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms.

NOTE. A causal association between antimicrobial use and the emergence of antimicrobial resistance has been reviewed elsewhere and is strongly suggested on the basis of several lines of evidence that are derived from patient and population levels of analysis, colonization, infection data and retrospective/prospective studies.

6. Barriers and Gaps

Following may be few points which resulted in emergence of antibiotic resistance:

1- Non availability or non-adherence to antibiotic usage policy. Strict adherence to clinical guidelines based on culture data, optimal dosing and duration are critical.

2- Attitudes and diagnostic uncertainty are key drivers of drug use and misuse. Gaps in the knowledge and perception among different prescriber categories exist due to inadequate or nonexistent continuing education requirements concerning infection control and antibiotic utilization for most health professionals.

3- Financial incentives which foster misuse of antibiotics; Aggressive marketing of antibiotic to both physicians and patients.

4- Misuse of antibiotics:

a. Use of antibiotics to treat symptoms that are clearly viral in nature.
b. Reliance on excessively broad-spectrum antibiotics when narrower-spectrum agents would be more appropriate.
c. Widespread use of antibiotic injections when not clinically indicated.

Way Forward

Despite these formidable barriers, it is the local nature of the problem which provides optimism that resistance can be contained and curbed if susceptible microbes can be re-established within defined areas. Individual institutions and health practitioners that use antibiotics more prudently will restore bacterial equilibrium in favor of susceptible bacteria and thereby preserve the effectiveness of antibiotic therapy in their communities.

While the WHO Global Strategy provides a thorough and comprehensive foundation, it is up to each nation, local institution and local provider to tailor specific initiatives to their particular resistance problems, resources and practices.

The literature now documents that institutional initiatives can dramatically reduce the prevalence of antibiotic resistance. The strict enforcement of antibiotic usage policies in hospitals can achieve a drastic reduction in the incidence of resistant organisms. Some specific recommendations in the Strategic Framework include:

Rational use of antibiotics:

a. Strict adherence to antibiotic usage guidelines
b. Do not use broad-spectrum antibiotics when narrower-spectrum agents would work as well.
c. Base the antibiotic prescription on culture results whenever possible.
d. Modify the regimen over time as required
e. Follow specific disease management pathways and algorithm

2- Consider cost-effectiveness in choosing an antibiotic regime.
3- Initiate infection control and antibiotic stewardship awareness activities among health care workers.
4- Prospective clinical audit with intervention and feedback, at both an individual patient and a prescriber level.

5- VACCINATIONS. As vaccines do not provide complete protection, or protection against other water/food borne infections following preventive strategies should be followed:
6- Regular hand washing practices.
7- Boiling of water before consumption.
8- Avoid foods and beverages from street vendors.
9- Ask for drinks without ice unless the ice is made from boiled or treated water.
10- Avoid flavored ice and juice because they may have been made with contaminated water
11- Choose hot foods: Eat foods that have been thoroughly cooked.
12- Control of flies: Ensure that cooked food is covered to protect it from flies.
13- Avoid meat which is undercooked.

It is the combined efforts of individual interventions that will become the global solution

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