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Short Communication

Antimicrobial and Antidiarrheal drugs Survey

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ABSTRACT

Diarrhea is a major health problem throughout the world and it has become more problematic in developing countries like Ethiopia. People, in several parts of the world, use different traditional medicines for treating diarrhea and it has been reported that the roots, leaves, and flowers of various species are used for the same purpose. Diarrhea is the second most common cause of death in children under five years. It causes more than 5-8 million deaths each year in infants and children below 5 years old. An antimicrobial is an agent that kills microorganisms or stops their growth. Antimicrobial medicines can be grouped according to the microorganisms they act primarily against. For example, antibiotics are used against bacteria, and antifungals are used against fungi. Antimicrobial resistance (AMR) is the ability of microorganisms to persist or grow in the presence of drugs designed to inhibit or kill them. These drugs, called antimicrobials, are used to treat infectious diseases caused by microorganisms such as bacteria, fungi, viruses and protozoan parasites.

Keywords: Antibiotics, microorganisms, protozoan parasites

INTRODUCTION

In today's world people's lifestyle gets complicated with some unhygienic conditions which usually increase the chances of various infections or infectious disease. To treat the infectious disease, there are various medicines which are prescribe in the single form or in the form of fixed dose combination. Some fixed dose combinations are providing the advantage of combination therapy i.e. reducing the pill burden, reduce the number of tablets or medication which taken by patient, and simple dosage schedule. Some fixed dose combinations have unnecessary financial burden, increase adverse effects and decrease quality of life. [1]

Fixed dose combination (FDC) is defined as "A combination of two or more active ingredients in a single dosage form in a fixed ratio of doses." FDC products are acceptable when the dosage of each ingredient meets the requirement to the population, and the combination has a proven advantage over single compounds which are administered separately in therapeutic effect, safety and compliance. World Health Organization (WHO) essential medicine list (EML) 2013 includes 24 FDCs. [2] A 'Fix Dose Combination (FDC)' is a combination of two or more active ingredients in a fixed ratio of doses. This term is used generically to mean a particular combination of active ingredients irrespective of the formulation or brand.

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(FDC) comprises of two or more active drug in a single dosage form.[3]

Definitions:

1. (FDC) is defined as "A combination of two or more active ingredients in a single dosage form in a fixed ratio of doses[3]
2. (FDC) is defined as " A large number of pharmaceutical preparations contain two or more drugs in a fixed dose ratio." [4]
3. (FDC) defined as " Fixed dose combinations products are medicines which contain two or more active ingredients in a fixed dose proportions in the same formulations.[5]

Advantages of FDC

1. FDCs are reduce the pill burden by reducing the number of pills to be taken by the patient.
2. FDCs reduce the adverse drug reaction with compared to higher dose of monotherapy.
3. Lead to reduction in overall cost.
4. Use to target a single disease or multiple disease
5. Certain drug combinations are synergistic, e.g. sulfamethoxazole + trimethoprim; levodopa + carbidopa/benserazide; combination oral contraceptives, isoniazid + rifampin.
6. The therapeutic effect of two components are being same may add up while the side effects are not different. For this the components of the FDC should act by different mechanisms, e.g. amlodipine + atenolol as antihypertensive.
7. The side effect of one component may be counteracted by the other, e.g. a thiazide + a potassium sparing diuretic. However, the amount of the latter may not be sufficient in all cases.
8. Combined formulation ensures that a single drug will not be administered. This is important in the treatment of tuberculosis, HIV-AIDS and falciparum malaria.[4]

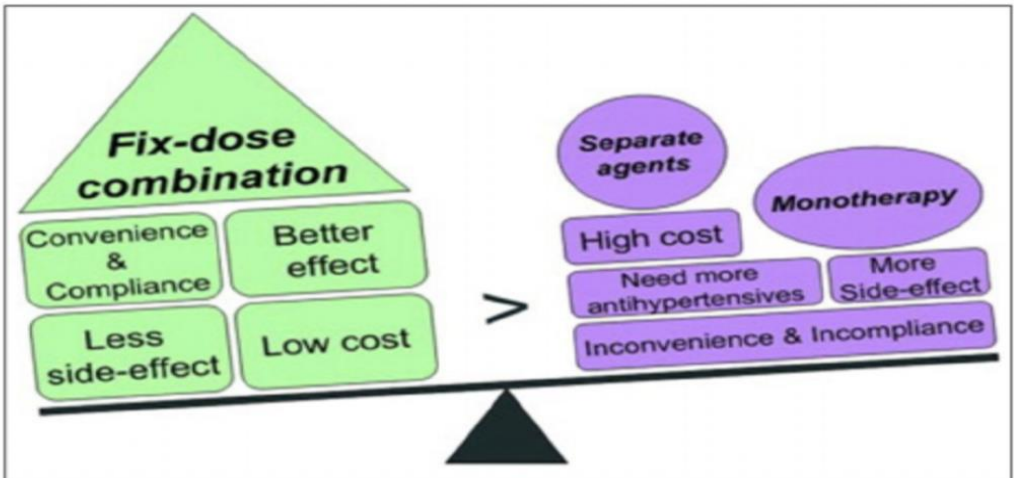


Fig-1 Advantages of fixed dose combinations compare to monotherapy.

Disadvantages of FDC

1. FDCs are may not available with the exact required combinations of the drugs for the patient.
2. The patient may not actually need all the drugs present in a combination:
3. The dose of most drugs needs to be adjusted and individualised. When a combined formulation is used, this cannot be done without altering the dose of the other components. Few combinations are available at more than one dose ratios, e.g. Levodopa (100 mg) + Carbidopa (10 mg or 25 mg).
4. The time course of action of the components may be different: administration of them at the same intervals may be inappropriate.[4]

The FDCs are available in all categories, many FDCs are bizarre combinations. Some therapeutic combinations have higher number of FDCs i.e. cough, cold and fever preparations, analgesic, antimicrobial, and muscle relaxants. The FDCs are should be developed for efficacy, safety, good therapeutic outcome, better patient compliances and less adverse drug reactions.[6]

Rational use of medicine:

Patients receive medicines appropriate to their clinical needs for an adequate period of time and at the lowest cost to them and their community. This

means correct drug should be chosen based on the efficacy, safety and cost for appropriate indication.

Rational FDCs e.g. Inj. Piptaz (Piperacilline + Tazabactum)

Tab Moxclav (Amoxicillin+ Potassium clavolanate)

Irrational use of medicine:

1. Polypharmacy: The use of too many medicines in a single patient.
2. Inappropriate use of antibiotics, often in adequate dosage or the use of antibiotics for non-bacterial infections like viral infections.
3. Over-use of injections when the oral route would be more appropriate.
4. Inappropriate self-medication

e.g. Ampiclox (Amoxicillin + Dicloxacillin)
Tinidazole+Ciprofloxacin

Why is Irrational use of medicines a problem?

It has been estimated that more than half the medicines used worldwide are prescribed, dispensed or sold inappropriately and that more than half of the patients do not take their medicines as prescribed by the doctor. Therefore, the irrational use of medicines is very serious global public health problem costing countries and patients a large amount of money. It causes increase in adverse drug reactions, and antibiotic resistance. Irrational over-use of medicines can also stimulate inappropriate patient demand, leading to reduce access, poor patient attendance and frequent stock –outs. The natural history of an illness also make it difficult at time separate the cause and effects, thus leading to irrational use. Pharmaceutical advertising also plays a huge role in promoting irrational use of medicines. [4]

Categories of fixed dose combination product:

Fixed dose combinations are classified into some class. Some FDCs are accepted as widely rational FDCs on the basis on their pharmacological actions on the target group of patients. eg. Levodopa with carbidopa use in the treatment of Parkinson disease. Mixture of drugs which are benefit only in few patients. eg. Multicomponent antacid mixtures Combinations of drugs for chronic disease in which multiple drug are recommended. i.e. HIV and AIDS [9]

Understanding the Role of Essential Medicines and use of WHO EML (World Health Organization Essential Medicine List)

Definition of Essential Medicines: The short definition of essential medicines according to the Word Health Organisation (WHO) is That the medicines are satisfy priority healthcare needs of a population [7].

Selection of Essential Medicines:

Essential medicines are selected based on public health such as the disease prevalence in the region / country, scientific evidence of efficacy, safety and cost effectiveness. Selection of essential medicines list is done at the level of healthcare provided, the knowledge, skills and training of the healthcare personnel involved, ease of administration of medicines. Thus they are mixture of evidence based criteria and factors relating to the healthcare system.[7]

The EML OF The WHO:

The model list of the WHO serves as a guide for national and institutional lists and is not meant as a global list. The method of selection can be applied by all countries. The drugs which are into the list have undergone major changes. First of all the, drugs were added or deleted on the based on experience of the expert members of the committee. For this the application form is submitted. The form has 15 questions and the application is made for public comment on the WHO website on medicines. The information available is very useful for healthcare professionals, specially for pharmacists and has been detailed information in the application and the comments. An expert international committee is constituted every two years.[7]

National List of Essential Medicines: The WHO EML is a model list. The decision about which medicines are essential remains a national responsibility based on the country's disease burden, priority health concerns, affordability concerns etc. Ministry of Health and Family Welfare, Government of India prepared and released the first National List of Essential Medicines of India in 1996 consisting of 279 medicines. This list was subsequently revised in 2003 and had 354 medicines. Later in 2011, the list was revised and had 348 medicines. since June 2018, 851 medicines (including 4 medical devices i.e. Cardiac stents, drug eluting stents, condoms and intra uterine devices) are regulated under Revised Schedule - I based on National List of Essential Medicines, 2015 (NLEM, 2015). To access the complete NLEM 2015,[7]

Purpose of the National List of Essential Medicines

The NLEM may have multiple uses.

It can:

- Guide safe and effective treatment is the priority disease conditions of a population.
- Promote the rational use of medicines.
- Optimize the available health resources of a country It can also be a guiding document for:

- State governments to prepare their list of essential medicines.
- Procurement and supply of medicines in the public sector.

The criteria are as follows

- The medicine should be approved in India.
- The medicine should be useful in disease which is a public health problem in India.
- The medicine have proven efficacy and safety profile based on valid scientific evidence.
- The medicine should be cost effective.
- The medicine should be aligned with the current treatment guidelines for the disease.
- The medicine should be stable under the storage conditions in India.
- When more than one medicine is available from the same therapeutic class, preferably one prototype/ medically best suited medicine of that class to be included after due deliberation and careful evaluation of their relative safety, efficacy, cost-effectiveness.[7]

Fixed Dose Drug Combinations: Issues and Challenges

The problems with fixed dose combinations: Pharmacodynamic mismatch between two components, one drug has antagonist effect which reduce efficacy or enhanced toxicity. Pharmacokinetic mismatch, in which drug have peak efficacy at different time. Drug interactions because of the common metabolizing pathways.

Very few fixed dose combinations in essential list of medicines. Essential medicines are satisfying the priority health care needs of the population. The list is prepared with the consideration to disease prevalence, efficacy, safety and cost effectiveness of medicines. Total 414 medicines in the 19th list of World Health Organization Essential Medicines list, out of them 27 are FDCs .

The Good, the Bad and the Ugly of the fixed dose combinations in India.

The Good FDCs – carbidopa + levodopa, sulfonamides + trimethoprim, antitubercular drugs, antiretroviral drugs, some antihypertensives, and some antidiabetic medications; The Bad FDCs – Do not add any value to the therapeutic usefulness and whose justification is debatable. Majority of the available FDCs fall in this category. Some examples are combinations of dual nonsteroidal anti-inflammatory drugs (NSAIDs), NSAIDs with muscle relaxant, and NSAIDs with H2 blockers; The Ugly FDCs – those that have neither evidence nor theoretical justifications. There are possibility of adverse event because of wrong administration of an unnecessary component, or where the dose titration is required. Some examples of such bizarre combination.[8]

Status of FDCs globally and in INDIA

FDCs are used worldwide. A large number of pharmaceutical preparations are contained two or more drugs in a fixed dose ratio. FDCs are enhance the efficacy of individual drugs, decrease the chances of drug resistance (eg Antimicrobial drugs), improve patient compliance and decrease the pill burden of the patients. There are some disadvantages associated with the use of FDCs like irrational prescriptions of FDC, ineffective and unsafe treatment, prolongation of illness and higher treatment costs.[3]

In a country like India, in past more than 85,000 commercial formulations were available either as single drug formulations or FDCs. As per the Drugs and Cosmetic Act, 1940, any new drug and the permission to market a drug is to be given by the Drugs Controller General of India (DCGI). As per rule 122(E) of the Drugs & Cosmetic Rules, 1945, the same criteria hold good for US markets as well. In 2008, estimated FDC market in India was about Rs. 3,000 crores to 3,500 crores. Parliamentary standing committee on health and family welfare noted that a very large number of FDCs are introduced into Indian market without prior clearance from CDSCO. The end result is that many FDCs in the market have not been tested for efficacy and safety. Overall due to all these reasons in September 2018 around 349 FDCs are banned.[5] The FDCs are treated as a new drug, because by the combination method of two or more drugs, some criteria may be change i.e. the safety, efficacy, and bioavailability of the individual Active Pharmaceutical Ingredient (API). As per the Drugs and Cosmetic Act, 1940, the permission of a new drug is given by the Drugs Controller General of India (DCGI). As per rule 122(E) of the Drugs & Cosmetic Rules, 1945, the same criteria holds good for US markets as well. More than one-third of all the new drug products which is introduced worldwide during the last decade were fixed dose combination (FDCs) preparations. The trend varied from country to country. In Japan, only 10 percent of the new products were fixed dose combinations out of total drug categories whereas, in European countries like Spain, the FDCs are was up to 56 percent.[11][12]

Classification of antimicrobial drugs

1. Sulphonamides and related Drugs.

eg Sulphamethoxazole

2. Trimethoprime and pyrimethamin
3. Quinolones

eg. Fluoroquinolones
Norfloxacine
Ciprofloxacine

4. B- lactum anti biotics:

eg. Penicillin
Cephalosporin

5. Tetracycline:

eg. Doxycycline
Monocycline

6. Aminoglycosides:

eg. Streptomycin
Getamycin

7. Azole Derivatives:

eg.Clotrimazole
Fluconazole
ketoconazole

Classification of antidiarrbeal drugs.

1. Antidiarrheal:

Eg. Ofloxacin
Ciprofloxacin

2. Imodium

eg loperamide

3. Azole derivateives

eg. Metronidazole

4. Antisecretory:

eg. Salphasalazine[4]

Following are some examples of antimicrobial FDCs which are banned in September 2018

1. Amoxicillin + Cefixime + Potassium Clavulanic Acid
2. Amoxicillin + Dicloxacillin
3. Amoxicillin 250 mg + Potassium Clavulanate Diluted 62.5
4. Amoxycillin + Dicloxacillin + Serratiopeptidase
5. Amoxycillin + Tinidazole
6. Azithromycin + Acebrophylline
7. Azithromycin + Ambroxol
8. Azithromycin + Cefixime
9. Azithromycin + Cefpodoxime
10. Azithromycin + Levofloxacin
11. Azithromycin + Ofloxacin
12. Cefixime + Levofloxacin
13. Cefixime + Linezolid
14. Cefpodoxime Proxetil + Levofloxacin
15. Cefuroxime + Linezolid
16. Cephalexin + Neomycin + Prednisolone
17. Combikit of Azithromycin, Secnidazole and Fluconazole
18. Combikit of Fluconazole Tablet, Azithromycin Tablet and Ornidazole Tablets
19. Oflaxacin + Ornidazole Suspension
20. Ofloxacin + Clotrimazole + Betamethasone + Lignocaine
21. Ofloxacin + Metronidazole + Zinc Acetate
22. Ofloxacin + Nitazoxanide

Methodology:

This is a Cross -sectional Study.

The human participants were not involved, the period of this study was 6 months.

Source of data: (IDR) Indian Drug Review, 2017, 2018. Total 138 FDCs were collected. Total 181 prescriptions were collected and evaluated.

Methodology: Rationality of Antimicrobial and Anti-diarrheal FDCs enlisted in IDR 2017 and 2018 were assessed with the help of a pre-validated tool. (Attached as Annexure 1). This tool is designed using WHO guidelines for registration of fixed dose combination medicinal products. The tool consists of eight point criteria which includes Active Pharmaceutical ingredients (API) with its strength, efficacy and safety. The evidence for efficacy and safety of the individual API and their combination were searched using standard textbooks, reference books of pharmacology and medicine. In addition, authentic web sources like Pub med data base, Google scholar and Cochrane data base have been used.

Inclusion: All FDCs (Anti-microbial and Anti diarrheal included in IDR of 2017 and 2018 , The prescriptions collected and evaluate.

Plan of Statistical Analysis: Data analysis was done using appropriate statistical test especially in percentage and frequency. Data were entered in Microsoft excel sheet and analyzed using appropriate statistical test.

Tool is use.

Shah S, Patel J, Desai M, Dikshit RK. Critical analysis of Antimicrobial and respiratory fixed dose combinations available in Indian market. International Journal of Medicine and Public Health. 2015;5(2):161-164.

METHODOLOGY BY USING TOOL

1. Active pharmacological ingredient along with strength …… …… ……

2. API

API

1 Approved by DCGI Yes (+1) No (−1)

2 Ingredient: Banned or controversial Yes (−1) No (+1)

API = Active pharmacological ingredient, DCGI = Drug controller general of India

3. Listing in EML WHO/National/Both/None (+1) (0)

4. Efficacy (text book/reference book/pub med/Medline/ other)

1 API Yes (+1) No (0)

2 FDC Yes (+1) No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

5. Safety (text book/reference book/pub med/Medline/other)

1 API Yes (+1) No (0)

2 FDC Yes (+1) No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

6. Pharmacokinetic (absorption/distribution/metabolism/ excretion/BA/BE/t ½)

• Interaction Favorable/Unfavorable/Not affected (+1) (−1) (0)

7. Pharmacodynamic- M/A of each ingredient Similar (0)/Different (+1)

8. Advantage of FDC

• Reduced Yes (+1)/No (0)

• Less ADR Yes (+1)/No (0)

• Convenient (frequency or pill count) Yes (+1)/No (0)

Total score:12

Score ≥7: Rational FDC

Score ≤6: Irrational FDC

The prevalidated tool was used. The tool considered of eight point criteria. The criteria in the tool included active pharmaceutical ingredients with safety and efficacy of each ingredients of fixed dose combination approval by regulatory authority, the criteria also included that fixed dose combinations enlisted in world health organization essential medicine list (WHO) EMLor in national essential medicine list (NLEM). The evidence of safety and efficacy of the individual ingredient of for fixed dose combination was searched by using standard textbooks and reference books. As per tool the criteria was scored plus (+1) for positive or minus for (-1) for negative or unfavorable condition. If the score was ≥ 7 then it was considered as rational, and if the score was ≤ 7 then it was considered as irrational. In this tool the (2017) 20th EML list was used. The data were entered in Microsoft excel sheet.

[Shah S, Patel J, Desai M, Dikshit RK. Critical analysis of Antimicrobial and respiratory fixed dose combinations available in Indian market. International Journal of Medicine and Public Health. 2015;5(2):161-164.]

Cefixime + Azithromycin

1. Active pharmacological ingredient along with strength …… …… ……

2. API

API

2.1 Approved by DCGI No (−1)

2.2 Ingredient: Banned - controversial Cefixime No (+1)
Azithromycine No(+1)

API = Active pharmacological ingredient, DCGI = Drug controller general of India

3. Listing in EML WHO/National/Both/None (0)

4. Efficacy (text book/reference book/pub med/Medline/ other)

4.1 API Cefixime (200mg) Yes (+1)
Azithromycine(250mg) Yes(+1)

4.2 FDC No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

5. Safety (text book/reference book/pub med/Medline/other)

5.1 API Cefixime(200mg) Yes (+1)
Azithromycin(250mg) Yes(+1)

5.2 FDC No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

6. Pharmacokinetic (absorption/distribution/metabolism/ excretion/BA/BE/t ½)

• Interaction Unfavorable (−1)

7. Pharmacodynamic- M/A of each ingredient similar Yes (+1)

8. Advantage of FDC

• Reduced No (0)

• Less ADR No (0)

• Convenient (frequency or pill count) No (0)

Total score: 5

THE TOTAL SCORE IS <6 so it is semi-rational FDC

Semi-rational FDC

ARTESUNATE +MEFLOQUINE

1. Active pharmacological ingredient along with strength …… …… ……

2. API

	API	
1	Approved by DCGI	Yes (+1)
2	Ingredient: Banned or controversial	Artesunate No (+1) Mefloquine No (+1)

API = Active pharmacological ingredient, DCGI = Drug controller general of India

3. Listing in EML — WHO/National/Both/None (+1)

4. Efficacy (text book/reference book/pub med/Medline/ other)

1	API	Artesunate Yes (+1) Mefloquine Yes (+1)
2	FDC	Yes (+1)

API = Active pharmacological ingredient, FDC = Fixed dose combination

5. Safety (text book/reference book/pub med/Medline/other)

1	API	Artesunate Yes (+1) Mefloquine Yes (+1)
2	FDC	Yes (+1)

API = Active pharmacological ingredient, FDC = Fixed dose combination

6. Pharmacokinetic (absorption/distribution/metabolism/ excretion/BA/BE/t ½)

- Interaction — Not affected (0)

7. Pharmacodynamic- M/A of each ingredient Similar (+1)

8. Advantage of FDC

- Reduced dose — No(0)
- Less ADR — No (0)
- Convenient (frequency or pill count) — Yes (+1)

Total score:12

Rational FD

Cefpodoxime + Levofloxacin

Thus, these 3 FDCs which are evaluated by tool.

1. Active pharmacological ingredient along with strength …… …… ……
2. API

API

1 Approved by DCGI — No (−1)
2 Ingredient: Banned or controversial — Cefpodoxime No (+1); Levofloxacin No (+1)

API = Active pharmacological ingredient, DCGI = Drug controller general of India

3. Listing in EML — WHO/National/Both/None (0)
4. Efficacy (text book/reference book/pub med/Medline/ other)
   1 API — Cefpodoxime Yes (+1); Levofloxacin Yes (+1)
   2 FDC — No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

5. Safety (text book/reference book/pub med/Medline/other)
   1 API — Cefpodoxime Yes (+1); Levofloxacin Yes (+1)
   2 FDC — No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

6. Pharmacokinetic (absorption/distribution/metabolism/ excretion/BA/BE/t ½)
   • Interaction — Not affected (0)
7. Pharmacodynamic- — M/A of each ingredient Different (0)
8. Advantage of FDC
   • Reduced — No (0)
   • Less ADR — No (0)
   • Convenient (frequency or pill count) — No (0)

Total score: 5

Semi- Rational

Result by using tool: Out of 138 FDCs, 102 belongs to antimicrobial group and 36 belongs to antidiarrheal group. Out of the total 46 (45 %) rational and total 10 (27 %) were rational. The mean rationality score of antimicrobial FDCs was 7.72 ± 0.33 while that of antidiarrheal FDCs was 7.5 ± 0.78. Majority of antimicrobial contained two active pharmaceutical ingredients (87) while antidiarrheal FDCs (17) contained 2 active ingredients active ingredients, (13) FDCs contained 3 active pharmaceutical ingredients and (6) FDCs contained >=4 [Table 1]. The rationality score for 12 antimicrobial FDCs listed in WHO EML was > 10 [Table 2]. In other addition, there were 2 others antimicrobial FDCs scored ≥8 as per tool.

Differentiate rational and irrational FDCs

Fixed dose combinations	Total	Rational	Irrational
Antimicrobial	102	46(45%)	56 (55%)
Antidiarrheal	36	10 (27%)	26 (73%)

Assessment of antimicrobial and antidiarrheal FDCs using rationality tool.

Parameters	**Antimicrobial FDCs**	**Antidiarrheal FDCs**
Number of rational FDCs	46(45%)	10 (27 %)
Number of irrational FDCs	56 (55 %)	26 (73%)
Mean rationality score	7.72 ± 0.33	7.5 ± 0.78

FDCs enlisted in WHO EML	14 (14%)	None
DCGI approved FDCs	54 (53%)	10 (27%)
Minimum score	3	3
Maximum score	17	18
Number of APIs in each FDCs 2 3 >=4	 87 15 0	 17 13 6

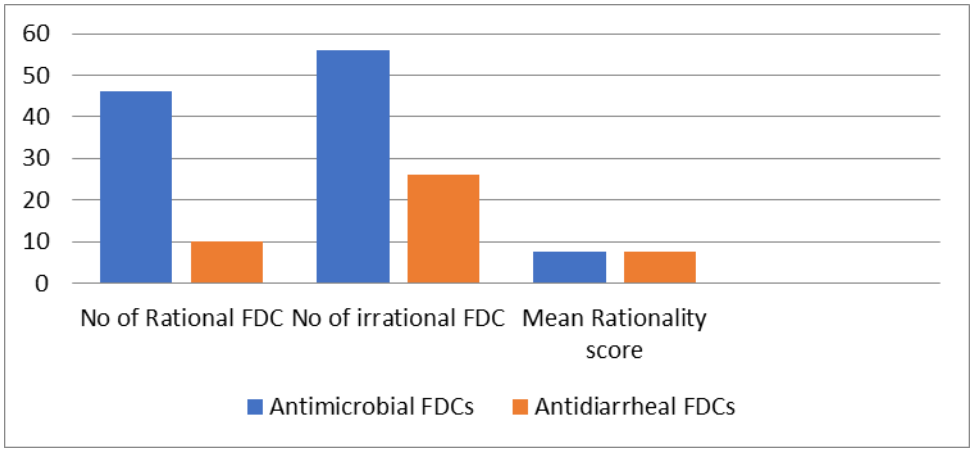


Fig. 2 Number of rational and irrational FDCs

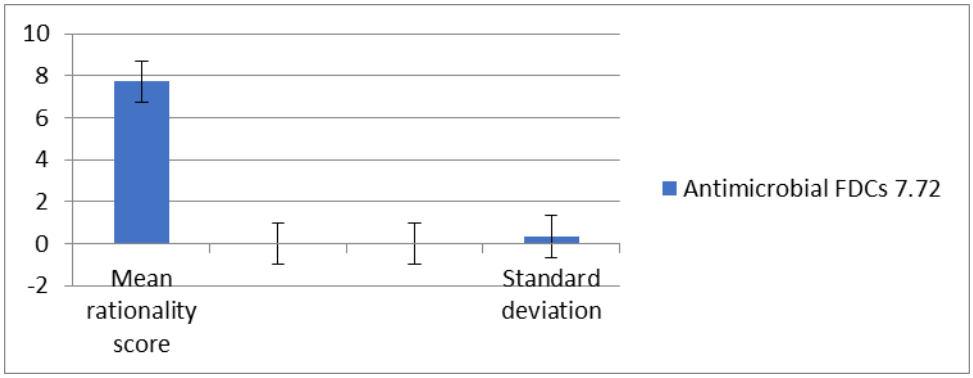


Fig. 3 Mean rationality score of antimicrobial FDC

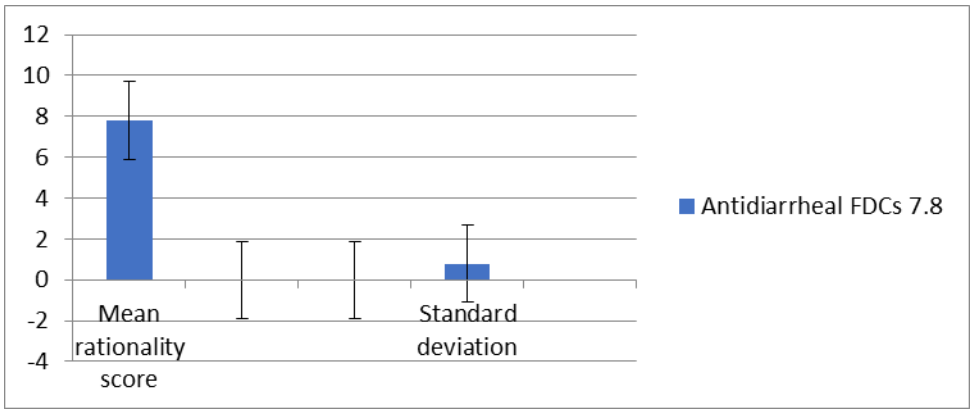


Fig. 4 Mean rationality score of antidiarrheal FDC

The FDCs which were rational as per tool and as well as enlisted in 20th WHO EML 2017

List of FDCs scored >=7 (rational) as per tool and enlisted in WHO EML 2017 (n=14)	
Antimicrobial FDCs (n=14)	
Tenofovir + Lamivudine +Efavirenz	Trimethoprime + Sulphamethoxazole
Lamividine + Zidovudine	Piperacilline +Tazobactum
Atazanavir + Ritonavir	Amoxicillin+ Clavulanic acid
Lopinavir+ Ritonavir	Artesunate +Amodiquine
Lamivudine + Zidovudine + Nevirapine	Tenofovir +Emtricitabine
Sulphadoxine+ Pyrimethamine +Artesunate	Tenofovir +Emtricitabine +Efevirenz
Artemether + Lumefantrine	Artesunate+ Mefloquine
Antidiarrheal FDCs (n=0)	
None	

Total 102 antimicrobial FDCs were evaluated, But only 11 FDCs were listed in WHO EML 2017. Total 36 antidiarrheal FDCs were evaluated but none of them were listed in EML. Out of 102 antimicrobial FDCs , 49 FDCs were rational and 53 FDCs were irrational. Out of antidiarrheal FDCs total 10 FDCs were rational and 26 were irrational. Majority of the rational anitimicrobial FDCs were antiretroviral , and antibacterial plus antiamoebic. Out of 36 antidirrheal FDCs , 10 were rational and 26 were irrational. None of them were listed in WHO EML 2017.

FDCs which were rational but not listed in WHO 20th EML 2017.

List of FDCs scored >=7 (rational) as per tool (according to our study) and not enlisted in WHO EML 2017	
Antimicrobial FDCs (n=11)	
Ceftriaxone + Tazobactum	Cephalexin +Bromhexin
Meropenem + Salbactum	Cephalexin +Carbocistine
Imepenam +Cilastatin	Amoxicillin + Clavulanic acid
Ticarcilin +Clavulanic	Tenofovir +Lamivudine
Cefotaxime +Salbactum	Lavudine +Stavudin+Nevirapine
Ceftriaxone+Salbactum	
Antidirrheal FDCs (n=5)	
Loperamide +Simethicone	
Lactobacillus i million cells +Sacchromyces bauldri + Zinc enriched yeast	
Sacchromyces baulardii + Lactobacillus + Zn + Yeast	
Lactobacillus +Thiamin +Riboflavin +Pyridoxine +Nicotinamide	
Lactobacillus acidophillus + Lactobacillus Rhamnos + bifidobectrum longum	

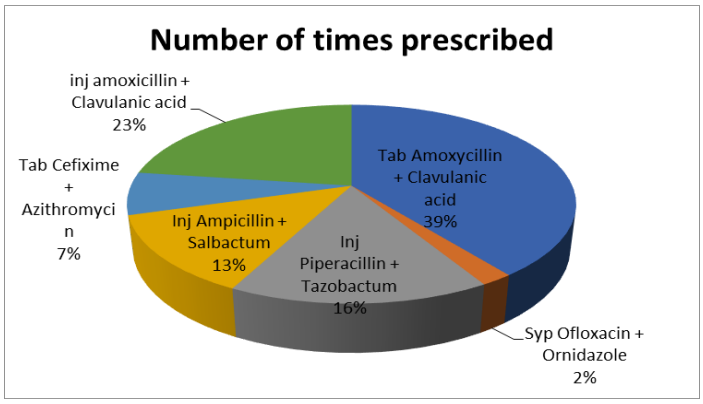
There were some FDCs in the above table which were not enlisted in the essential medicine list but rational on their good therapeutic outcomes and less adverse drug reactions, total 11 antimicrobial rational FDCs which were not enlisted but still rational. As well as 10 antidiarrheal FDCs were rational but none of them were listed in essential medicine list.

Using prescription method: There are 181 prescriptions evaluated by the above tool. A total of 181 prescriptions were collected from hospital store, out of these, FDC were prescribed in 119 (65%) prescriptions. Some common rational and some irrational FDCs were observed which are given below table. Out of them total 92 (77%) were rational and 27 (23%) were irrational.

Total number of prescriptions	181
Number of single formulation prescribed.	88 (35%)
Number of FDCs prescribed.	119 (65%)
Rational FDCs	Tab Amoxicillin + Clavulanic acid Inj Amoxicillin + Clavulanic acid Inj Piperacillin + Tazobactum Inj Ampicillin + Salbactum
irrational FDC	Tab Cefuroxime + Clavulanic acid Tab Ofloxacin + Ornidazole Tab Cefixime + Azithromycin Tab Cefixime + Clavulanic acid

Fixed dose combination	Number of times prescribed
TabAmoxicillin +Clavulanic acid	40
Inj Amoxicillin + Clavulanic acid	23
Inj Piperacillin + Tazobactum	16
Inj Ampicillin + Sabactum	13
Tab Ofloxacin + Ornidazole	15
Tab Cefixime + Azithromycin	7
Tab Cefixime + Clavulanic acid	3
Syp Ofloxacin + Ornidazole	2

From evaluation of 181 prescriptions, there are rational fixed dose combinations are mostly prescribed. The rational FDCs like amoxicillin + aclavulanic acid, and Piperacillin + Tazobactum.
With those some irrational fixed dose combinations are also prescribed, and one of them the antidiarrheal Syrup. Ofloxacin + Ornidazole is recently banned in September 2018. The reason of irrationality of Ofloxacin with Ornidazole Combining (antiamoebic) with fluoroquinolone (antibacterial) is irrational because the patient suffers only from one type of diarrhoea. Using this combination adds to some high cost, adverse effects and may encourage resistance.



Number of times prescribed FDCs

Conclusion: Rationality assessment of antimicrobial and antidiarrheal FDCs reveals that a number of these FDCs in Indian market are irrational. From the study we come to know that there are lots of fixed dose combinations are available in Indian market from them few were evaluate by our study but only 45 % antimicrobial fixed dose combinations and 27 % antidiarrheal fixed dose combinations were rational. And 55 % antimicrobial and 72% antidiarrheal FDCs were irrational. This calls for a close scrutiny of marketed FDCs and educating prescribers to use them with great care and caution.

After the prescription study we conclude that rational FDCs are prescribed in majority but nowdays , because we can see that there were rational fixed dose combinations were prescribed in majority such as Tab. Amoxicillin + Clavualanic acid, Inj Piperacillin + Tazobactum but as well as some irrational were also prescribed in very few prescriptions For example syrup Ofloxacin with Ornoidazole which was recently banned in September 2018 by government so it need to some regulatory framework for drug manufacturing and marketing.

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