

Comparative Evaluation of Low Versus High Doses of Rifampin for the Treatment of Staphylococcal Bone and Joint Infections: an open-label, randomized, controlled non-inferiority trial (EVRIOS)



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EVRIOS Study Concept

Rifampin is essential for the treatment of staphylococcal infections in the presence of foreign bodies in animal models¹

In Humans, few prospective studies demonstrated the superiority of rifampin-containing regimens²

The optimal dosage for efficacy is unknown : 10 mg/kg qd, 20 mg/kg qd or 10 mg/kg bid, 900 mg qd...

The relationship between side-effects and dosage remains unclear

¹ K. Tshetu et al. Rev Infect Dis 1983

²Zimmerli et al. JAMA. 1998

Objective of the EVRIOS study



To compare high and low doses of rifampin, with a partner antibiotic, in the treatment of staphylococcal bone and joint infection, with or without orthopedic devices.



To understand the relationship between dosage and side-effects

Methodology (1) - Design



Open-label, randomized, controlled, noninferiority trial



Outcomes :

Primary : Failure defined as the persistence or recurrence of infection with the initial causative bacteria within 1 year after the completion of antibiotics.

Secondary : Serious adverse effect rates in the two allocated groups /Risk factors for failure



Number of patients
needed : 500

Hypothesis :

- Global efficacy 80%
- 10% loss to follow up
- 10% absolute difference for non-inferiority

Methodology (2) - Allocation

Inclusion



Adults (> 18), inform consent,
Microbiologically confirmed bone and joint infections due to rifampin-susceptible *Staphylococcus sp.* with or without orthopedic device
Rifampin scheduled to be used for at least 14 days
45 < Weight < 145 kg

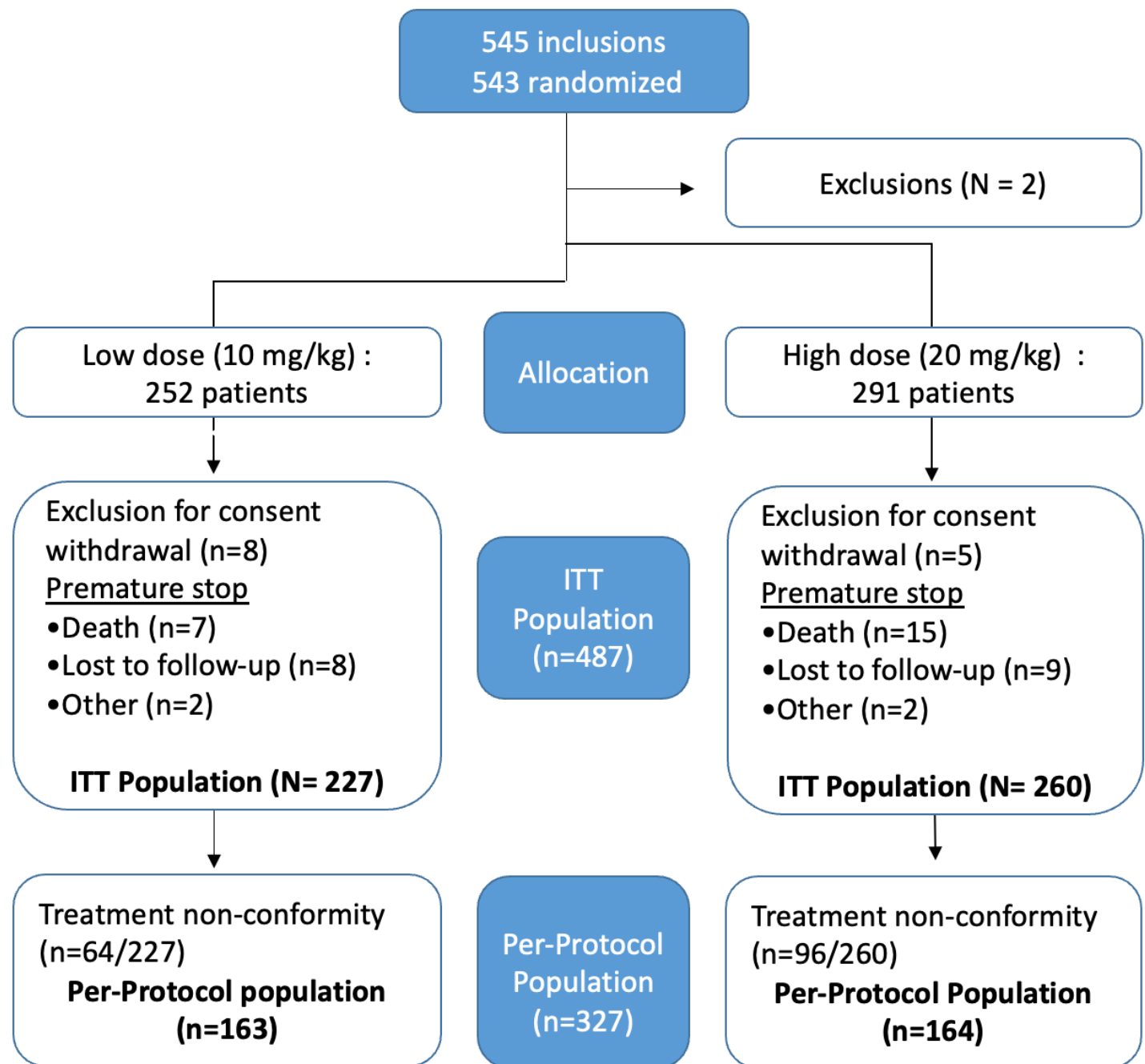
Randomization

Group 1 : rifampin 10 mg/kg (Low-dose) qd
Group 2 : rifampin 20 mg/kg (High-dose), qd or divided in 10mg/kg bid for high BMIs

Results



Flow-chart

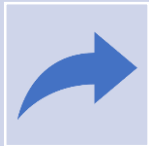


Population characteristics

(excluding consent withdrawals)

	Low dose (n=244) n/(%)	High dose (n=286) n/(%)
Mean age, - years	58.3 ± 16.4	61.0 ± 16.4
Male sex	177 (72.5)	203 (71.0)
Mean BMI, kg/m ²	27.5 ± 6.3	28.1 ± 5.4
Presence of orthopedic devices	117 (48)	144 (50.3)
<i>Prosthesis</i>	81 (33.3)	99 (34.6)
Diabetes	51 (20.9)	49 (17.1)
Microbiology		
- <i>S. aureus</i>	188 (77)	214 (74.8)
- <i>S. epidermidis</i>	34 (13.9)	47 (16.4)
- <i>S. lugdunensis</i>	12 (4.9)	17 (5.9)
- <i>S. capitis</i>	22 (9)	26 (9.1)
Duration of rifampicin treatment (in days)	43.9 ± 22.1	42.4 ± 23.6
Total duration (all antibiotics; in days)	59.2 ± 45.7	55.9 ± 36.4
Drug Companion		
- Levofloxacin/Ofloxacin	204 (83.6)	243 (85)
- Cotrimoxazole	38 (15.6)	47 (16.4)

ITT and Per Protocol Analysis

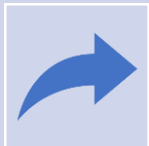


ITT
Treatment failure

Low-dose group : 8/227 (3.5% [1.5% - 6.8%])

High-dose group : 10/265 (3.8% [1.8% - 6.8%])

Risk difference, 0.0019 [-0.032 – 0.036]



Per-protocol
Treatment failure

Low-dose group : 6/163 (3.7% [1.4% - 7.8%])

High-dose group : 5/164 (3.0% [1.0% - 7.0%])

Risk difference, 0.0063 [-0.033 – 0.045]



Serious adverse events
linked to rifampin

Low-dose group : 1.6%

High-dose group : 7%

p= 0.0043

Per Protocol Tolerance analysis

AE's	Low dose (n=160)	High dose (n=162)	p
Loss of appetite	54 (33.8% [26.5% - 41.6%])	77 (47.5% [39.6% - 55.5%])	0.0118
Nausea	32 (20.0% [14.1% - 27.0%])	58 (35.8% [28.4% - 43.7%])	0.0016
Vomiting	11 (6.9% [3.5% - 12.0%])	21 (13.0% [8.2% - 19.1%])	0.0679
Itching	18 (11.3% [6.8% - 17.2%])	35 (21.6% [15.5% - 28.7%])	0.0122
Rash	8 (5.0% [2.2% - 9.6%])	19 (11.7% [7.2% - 17.7%])	0.0294
Tremor	7 (4.4% [1.8% - 8.8%])	20 (12.3% [7.7% - 18.4%])	0.0099
Any side effect at W6	2.6 ± 2.6	3.2 ± 2.8	0.0321



Strength

Large randomized study

PP and ITT analyses showing similar results.

Randomization has well-balanced the two groups in terms of risk factors (data not shown).



Limits

Not a double-blind study

- In the high-dose group, clinicians could feel more free to reduce rifampin dosage.

Treatment failure rates have been lower than expected

- Role of relatively low number of patients with orthopedic devices included.
- Standardized protocol follow up may improve outcome.



Take-Home messages

We can safely use Rifampin 10 mg/kg qd in bone infection.

- High success level
- Less side-effects compared to 20 mg/kg/day

EVRIOS doesn't answer many remaining questions:

- Can we use shorter regimens of Rifampin ?
- Shall we introduce Rifampin very early or shall we wait for the inoculum to be as low as possible ?

Acknowledgments

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St Malo
Angers
Caen
Lyon

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Back-up

Methodology - Analysis

- To demonstrate non inferiority :
 - Intent to treat (ITT) and per-protocol (PP) analysis of the primary endpoint, according to treatment allocation was carried out,
 - Using Dunnett and Gent's absolute difference tests (Non-inferiority test for two proportions)
- Univariate comparison analysis used :
 - Student's t test or Wilcoxon's t test for quantitative variables,
 - Chi2 test or Fisher's exact test for qualitative variables.
- Multivariate analysis used logistic regression models, through a stepwise regression with forward selection method
 - Variables include in the model were selected from univariate analysis, clinical relevance or evidence from previous published medical studies
- With the exception of the main criterion, all statistical tests had a significance level of 0.05.
- Statistical analyses were performed using SAS® 9.4 software (SAS Institute, Cary, NC, USA).