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# Linezolid treatment of nosocomial bacterial infection with multiresistant Gram-positive pathogens in preterm infants: a systematic review

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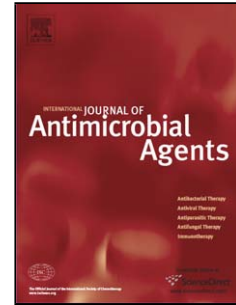
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1           **Linezolid treatment of nosocomial bacterial infection with**  
2           **multiresistant Gram-positive pathogens in preterm infants – a**  
3           **systematic review**

4  
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## 1 **Abstract**

2 Linezolid is an antibiotic of the oxazolidinone class that has bacteriostatic and  
3 bactericidal activity against a broad range of Gram-positive bacteria, including  
4 multiresistant pathogens. Due to increasing resistance of Gram-positive pathogens to  
5 traditional antibiotics like vancomycin the oxazolidinones were introduced into  
6 therapy. Aim of this review was to summarize actual data on pharmacokinetics,  
7 safety and clinical use of linezolid in preterm infants. MEDLINE and EMBASE were  
8 searched using the term “linezolid” combined with “newborn”, “neonate”, “preterm”  
9 and “premature” between 1988 and 2008. Studies reporting on a population  
10 including preterm infants and other age-groups and case reports on preterm infants  
11 only were acceptable for analysis. Five studies and eight case reports were identified  
12 evaluating linezolid in preterm infants. A dosage regimen of 10 mg/kg body weight  
13 given either orally or intravenously every 8 hours in infants aged one week or more  
14 and the same dose given every 12 hours in infants younger than one week was  
15 shown to be safe and effective with mean treatment duration of 10 to 28 days.

16 In summary linezolid has shown to be a safe and effective alternative to vancomycin  
17 in the treatment of infections with multiresistant Gram-positive pathogens in preterm  
18 infants.

19

20 Key words: linezolid, preterm infant, gram-positive bacteria, nosocomial  
21 infection

22

## 1 1. Introduction

2

3 Gram-positive pathogens are the most common and troublesome causes of  
4 nosocomial infections in neonatal intensive care units particularly coagulase-  
5 negative staphylococci (CONS) and enterococci<sup>1,2</sup>. Those pathogens  
6 accumulate with indwelling catheters and focal complications associated with  
7 prematurity and can be the cause for early- and more over late-onset sepsis<sup>3,4</sup>.  
8 Due to increasing resistance of these pathogens to traditional antibiotic therapy  
9 like ampicillin, aminoglycosides and cefotaxime, glycopeptides like vancomycin  
10 are often required for adequate therapy. Unfortunately it is assumed that the  
11 potential overuse of vancomycin might be dangerous (i.e., need for parenteral  
12 therapy with the risk of phlebitis or other injection reactions, unnecessary use of  
13 a nephrotoxic drug, increased risk of antibiotic resistance and possible  
14 colonization with multiply resistant organisms, fungi, or both)<sup>4</sup>

15 Therefore linezolid, a member of the oxazolidinones, a new class of antibiotics  
16 with a completely novel mechanism of action<sup>5</sup>, has become an alternative  
17 treatment option. Especially in glycopeptide-resistant Gram-positive bacterial  
18 infections and in cases of glycopeptide treatment failures linezolid has shown to  
19 be a potent second-line drug. Linezolid possesses excellent microbial activity  
20 against a wide variety of Gram-positive pathogens, with bactericidal effects  
21 against most strains of *Streptococcus* spp. and bacteriostatic action on  
22 *Enterococcus* spp. and *Staphylococcus* spp., including vancomycin-resistant  
23 enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and  
24 Methicillin Resistant Coagulase-Negative Staphylococcus (MRCNS)<sup>6, 7, 8, 9</sup>.  
25 Linezolid is also active against anaerobes, atypical microbes such as

1 Chlamydia and Mycoplasma spp., some rapidly growing mycobacteria and  
2 selected Gram-negative bacilli<sup>10,11, 12</sup>. Linezolid or N-([S]-[3-fluoro-4-  
3 morpholinophenyl]-2-oxo-5-oxazolidinyl) methyl) acetamide is a totally synthetic  
4 antimicrobial agent structurally unrelated to other agents with an unique  
5 mechanism of action<sup>6,7</sup>. Thus, cross-resistance with other protein synthesis  
6 inhibitors such as aminoglycosides and macrolides is generally avoided<sup>13</sup>.  
7 Moreover the development of resistance to linezolid seems difficult to achieve,  
8 requiring specific 23S recombinant RNA mutations<sup>14</sup>.

9 In the U.S. linezolid is approved for paediatric patients since December 2002.  
10 In Austria as in many other European countries its use in paediatric patients is  
11 off-label. Aim of this systematic review was to summarize actual data on  
12 pharmacokinetics and safety, as well as to outline experiences in clinical use of  
13 linezolid in preterm infants.

## 1 **2. Methods**

2

### 3 **2.1 Literature sources and search terms**

4 MEDLINE and EMBASE were searched systematically to identify all papers  
5 published in the English and German literature regarding the use of linezolid in  
6 preterm infants, including the period from January 1988 to June 2009. This time  
7 window was chosen due to the fact that all identified papers about the class of  
8 oxazolidinones and linezolid were published after 1987. For the search the  
9 following keywords were utilized both individually and in different combinations:  
10 linezolid, newborn, neonate, preterm and premature. Cross-referencing of  
11 important articles was also applied.

12

### 13 **2.2 Study selection**

14 Original observational or interventional population or hospital-based studies  
15 involving preterm infants < 37 weeks of gestational age with severe infections  
16 with multiresistant Gram-positive infections being treated with linezolid were  
17 included. In addition, only studies with well-defined participants' characteristics  
18 and number of subjects treated with linezolid were included in the analysis.

19

### 20 **2.3 Data abstraction**

21 One author extracted and screened potentially relevant articles to determine  
22 whether they met the inclusion criteria. Then data was abstracted from each  
23 included article and reviewed cross-referencing with the co-authors for  
24 additional potentially relevant articles. Abstract discrepancies were resolved by  
25 repeated review and discussion.

- 1 We extracted the following types of data from each study identified as specified
- 2 by our protocol: indications, pharmacokinetics and recommended dosage,
- 3 duration of treatment, efficacy and side effects.

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### 1 3. Results

2 A total of five pharmacological and/or clinical studies and eight case reports  
3 were identified. Data of pharmacological and clinical studies are summarized in  
4 table 1.

#### 6 **3.1 Pharmacologic properties in preterm infants**

7 In the manufacturer's prescribing information<sup>15</sup> the pharmacokinetic properties  
8 of single dose intravenous linezolid in paediatric patients are reported. Results  
9 are based on studies of linezolid 10 mg/kg in paediatric patients aged <7 days  
10 (gestational age <34 weeks [n=9], gestational age ≥34 weeks [n=10]), 7-28  
11 days (n=10), >28 days to 3 <3months (n=59), and 3 month to 11 years (n=59),  
12 and linezolid 600 mg or 10 mg/kg to a maximum to 600 mg in adolescent  
13 volunteers and patients aged 12-17 years (n=36)<sup>15</sup>. The pharmacokinetics in  
14 these age groups are compared with those in 29 adult subjects receiving a  
15 single intravenous infusion of linezolid (dose normalized to 600 mg)<sup>15</sup>. The  
16 studies showed that values including pharmacokinetic parameters (area under  
17 the plasma concentration-time curve [AUC], systemic clearance [CL] and  
18 elimination half-life [ $t_{1/2}$ ]) of linezolid change with increasing age (figure 1)<sup>15</sup>.  
19 Preterm neonatal patients aged <1 week demonstrated a higher mean AUC  
20 than the other age groups; however, there was no difference at the age of 7  
21 days.

22 In a similar manner, mean clearance for infants <7 days postnatal age is  
23 substantially less than in older infants and the CL of linezolid increases rapidly  
24 during the first week after birth in both preterm and full-term neonates<sup>16</sup>. Among  
25 preterm infants <7 days old the clearance of linezolid is lowest; clearance rates

1 are similar to those observed in adult patients. However, the clearance of  
2 linezolid increases markedly in the first week of life, regardless of gestational  
3 age, such that infants >7 days old have clearance values that are  $\approx$ 3-fold  
4 greater than those of adults (figure 1). The age-dependent differences in the CL  
5 of linezolid may be partially the result of differences with age in activity of non-  
6 CYP isoforms (e.g. amidases, peptidases and peroxidases), although these  
7 enzymes have not specifically been identified as playing a role in linezolid  
8 metabolism<sup>17,18</sup>. In contrast to AUC, CL and  $t_{1/2}$  the age of paediatric patients  
9 does not affect the  $C_{max}$  or steady-state volume of distribution ( $V_{SS}$ ) of  
10 linezolid<sup>15</sup>.

11 Kearns et al<sup>19</sup> reported the results from a multicenter study of linezolid  
12 disposition in preterm and term neonates and young infants. The population of  
13 42 infants was stratified into 4 subgroups: group 1 (n=9), gestational age <34  
14 weeks and postnatal age <8 days; group 2 (n=7), gestational age <34 weeks  
15 and postnatal age 8 days to 12 weeks; group 3 (n=11), gestational age >34  
16 weeks and postnatal age <8 days; and group 4 (n=15), gestational age >34  
17 weeks and postnatal age 8 days to 12 weeks. The study was conducted as an  
18 open label, single-dose evaluation of linezolid pharmacokinetics and tolerance  
19 at a single dose level (10 mg/kg). Single-dose linezolid was well tolerated in  
20 neonates and young infants in this study. There were no clinically significant  
21 adverse events or clinically significant changes in vital signs or physical findings  
22 associated with the study drug or experimental procedures. The  
23 pharmacokinetic parameters of the study are comparable with data reported  
24 above<sup>15,17</sup>.

### 1 **3.2 Recommended dosages and duration of treatment in preterm infants**

2 The recommended dosage of linezolid in most indications is 10 mg/kg every 8  
3 hours in children aged 0-11 years and 600 mg every 12 hours in adolescents  
4 aged  $\geq 12$  years<sup>15</sup>. Because CL is slower in preterm neonates (gestational age  
5  $< 34$  weeks) aged  $< 7$  days as well as in term neonates aged  $< 7$  days, a longer  
6 interval between doses (every 12 hours) is initially recommended in these  
7 patients; however, the clinical response should be assessed considering the  
8 site and severity of infection and the underlying medical condition. An 8-hour  
9 dosing interval may be used in preterm and term neonates under 7 days of life,  
10 if the response to linezolid is suboptimal and should be used in all neonates by  
11 7 days of age. This recommendation is supported by the results gained by  
12 Kearns' et al. in their multicenter study of linezolid disposition in preterm and  
13 term neonates and young infants<sup>19</sup>. Biedenbach and Jones have suggested the  
14 following breakpoints for linezolid: minimum inhibitory concentration (MIC)  
15  $\leq 4$  mg/L for susceptibility and  $\geq 16$  mg/L for resistance<sup>20</sup>.

16 No dosage changes are required when switching from intravenous to oral  
17 formula of linezolid. The recommended durations of treatment are 10-14 days in  
18 patients with skin and skin-structure infections or pneumonia and 14-28 days in  
19 those with vancomycin-resistant *E. faecium* infections<sup>15</sup>.

20

### 21 **3.3 Side effects – tolerability in preterm infants**

22 Kaplan et al<sup>21</sup> assessed the clinical efficacy and safety of linezolid vs.  
23 vancomycin in 316 hospitalized children including 34 preterm infants infected  
24 with nosocomial multiresistant Gram-positive bacteria. They were randomized  
25 2:1 to receive either linezolid iv 10mg/kg every 8 h or vancomycin iv 10 to 15

1 mg/kg every 6 to 24 h at least for 3 days followed by oral linezolid or  
2 vancomycin and then by an appropriate oral agent. Treatment duration was 10  
3 to 28 days. The overall clinical cure rate was 89% compared to 85% ( $p=0.31$ ).  
4 Pathogen eradication rates were high for both linezolid and vancomycin  
5 regarding methicillin susceptible *S. aureus* (95% vs. 83%,  $p=0.87$ ). Linezolid  
6 treated patients required significantly fewer days of iv therapy compared with  
7 vancomycin treated patients ( $8.0 \pm 4.8$  vs.  $10.9 \pm 5.8$ ,  $p<0.001$ ). In addition  
8 significantly fewer linezolid-treated patients had drug-related adverse events  
9 compared to vancomycin-treated patients (19% vs. 34%,  $p=0.003$ ) including  
10 rash, moniliasis, red man syndrome, pruritus and fever (see [Table 2](#))<sup>21</sup>.  
11 Hematologic effects were uncommon and similar between treatment groups.  
12 Details of the 34 preterm infants of the above mentioned study were reported by  
13 [Deville et al](#)<sup>22</sup> focussing on the results of a total of 63 newborns. Twenty-six preterm  
14 infants <34 weeks were in the linezolid group and compared to eight in the  
15 vancomycin group. The clinical cure rate was 84% compared to 77% ( $p=0.553$ ).  
16 Pathogen eradication rates comparing both groups were 67% vs. 60% ( $p=0.850$ ) for  
17 *S.aureus* and 88% vs. 100% ( $p=0.397$ ) for coagulase-negative staphylococci. Study-  
18 emergent adverse events were similar in both groups (76.7% compared with 73.7%,  
19  $p=0.795$ ). Drug-related adverse events were reported in 11.6% of linezolid-treated  
20 compared with 31.6% of vancomycin-treated infants ( $p=0.058$ ). Oral candidiasis was  
21 only observed in two of 19 (10.5%) vancomycin treated compared to none of the  
22 linezolid treated infants ( $p=0.031$ ). The percentage of patients with abnormal  
23 hematology or serum chemistry values was not statistically different between groups.  
24 However, more linezolid-treated patients had decreases in hemoglobin (linezolid  
25 23.3% vs. vancomycin 5.3%;  $p=0.087$ ) and hematocrit (linezolid 23.3 vs. vancomycin

1 5,  $p=0.172$ ) and increases in total bilirubin (linezolid 19.0% vs. vancomycin 10.5%,  
2  $p=0.405$ ).

3 Meissner et al<sup>23</sup> evaluated the occurrence of hematologic effects of linezolid  
4 compared to vancomycin in the same study group<sup>22</sup>. Overall, no significant  
5 differences were noted in drug-related hematologic events, such as  
6 thrombocytopenia (linezolid, 1.9% vs. vancomycin, 0%;  $P = 0.170$ ), anaemia  
7 (linezolid, 1.4% vs. vancomycin, 1.0%;  $P = 0.771$ ) or neutropenia (linezolid, 0% vs.  
8 vancomycin, 0%). No clinically relevant changes in reticulocyte index or iron studies  
9 were noted between treatment groups.

10

### 11 **3.4 Case reports**

12 In our literature review we found eight case reports on a total of 14 preterm  
13 infants successfully treated with linezolid. In all cases linezolid was applied after  
14 glycopeptide treatment failures with known or suspected glycopeptide-resistant  
15 Gram-positive bacteria. Seven patients suffered from ventriculitis or an infection  
16 of the cerebral spinal fluid (CSF). As linezolid has previously been shown to  
17 have excellent penetration into the CSF in adults<sup>24</sup>, it also achieved good  
18 concentrations in CSF in those preterm infants<sup>25,26,27</sup>. Another two patients  
19 suffered from endocarditis<sup>28,29</sup>, three patients suffered from peritonitis<sup>30</sup> or  
20 necrotizing enterocolitis<sup>31</sup>, one patient had nosocomial pneumonia (?)<sup>30</sup> and  
21 one child suffered from a persistent septicaemia<sup>32</sup>. In most cases glycopeptide-  
22 resistant Enterococcus faecium could be isolated. Other isolated pathogens  
23 where Methicillin-resistant Staphylococcus aureus (MRSA), Staphylococcus  
24 epidermidis, Staphylococcus haemolyticus or Staphylococcus capitis. In two  
25 cases there was a co-infection with Klebsiella oxytoca.

1 Dosage and duration of linezolid was according to the manufacturer's  
2 recommendations in 12 of 14 patients. Except for temporary thrombocytopenia  
3 in one patient no haematological or other laboratory or clinical side effects of  
4 linezolid were observed. In one patient dosage had been increased to 12 mg/kg  
5 every 8 without evidence of bone marrow suppression<sup>26</sup>, and even treatment  
6 over 9 weeks in one patient was well tolerated<sup>28</sup>.

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#### 1 **4. Conclusion**

2 In clinical studies comparing the efficacy and safety of linezolid versus  
3 vancomycin linezolid proved to be well tolerated and as effective as  
4 vancomycin in a total of 51 preterm infants. Adding the information out of eight  
5 case studies including 14 preterm infants linezolid demonstrated to be a safe  
6 and potent second-line drug in the treatment of nosocomial bacterial infection  
7 with multiresistant Gram-positive pathogens in preterm infants. Benefits of  
8 linezolid compared to vancomycin include its availability in equivalent  
9 intravenous and oral formula and its safer use in combination with  
10 aminoglycosides. Linezolid should be used as second-line treatment, but due to  
11 overwhelming nosocomial infections in very low birth weight infants its use  
12 might be considered earlier in case of unassertive clinical improvement of the  
13 baby or knowledge of multiresistant Gram-positive pathogens at the NICU.

14 Study results are limited by the low number of preterm infants included. Further  
15 prospective studies are needed to confirm the efficacy and safety of linezolid in  
16 the treatment of multiresistant Gram-positive infections in this particular  
17 vulnerable group of preterm infants. Additionally information on linezolid levels  
18 in plasma and cerebrospinal fluid is warranted.

19

## 1 **5. Recommendations**

2

3 Considering the available data on linezolid in preterm infants we recommend its use  
4 as second line antibiotic in preterm infants infected with glycopeptide-resistant  
5 bacteria and/or in case of glycopeptide treatment failures. However, in cases of  
6 known or suspected glycopeptide resistant pathogens we advise to consider linezolid  
7 at an earlier stage of treatment. A dosage regimen of 10 mg/kg body weight given  
8 either orally or intravenously every 8 hours in infants aged one week or more and the  
9 same dose given every 12 hours in infants younger than one week was shown to be  
10 safe and effective with mean treatment duration of 10 to 28 days. Due to the risk of  
11 myelosuppression weekly evaluation of complete blood counts is recommended.

12

### 13 **Funding**

14 None.

### 15 **Competing interest**

16 No competing interests are identified by any of the authors.

### 17 **Ethical approval**

18 This review needed no Ethical Approval.



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**Tables:****Table 1:** Summary of pharmacological studies, studies on tolerability and case studies on linezolid use in preterm children <sup>15,19,21-23,25-32</sup>

| Year | Age of patients | Number<br>Total/preterm | Dosage<br>(mg/kg) | interval | Duration    | Adverse<br>events (%) | Reference |
|------|-----------------|-------------------------|-------------------|----------|-------------|-----------------------|-----------|
| 2002 | PT, T, ≤ 17 y   | 136/9                   | 10                | 1 dose   | 1 d         | n. sp.                | 15        |
| 2003 | PT, T, ≤12 w    | 42/16                   | 10                | 1 dose   | 1 d         | n. sp.                | 19        |
| 2003 | PT, T, ≤ 12 y   | 215/26                  | 10                | 8 h      | 10-28 d     | 18.8                  | 21        |
| 2003 | PT, T, ≤11 y    | 215/26                  | 10                | 8 h      | 10-28 d     | 13.1                  | 22        |
| 2003 | PT, T, ≤ 90 d   | 43/26                   | 10                | 8 h      | 10-28 d     | 7.0                   | 23        |
| 2002 | 29 w            | 1/1                     | 10                | 8 h      | 21 d        | 0                     | 25        |
| 2007 | 35 w            | 1/1                     | 10                | 8 h      | 21 d        | 0                     | 26        |
|      |                 |                         | 12                | 8 h      | 14 d        |                       |           |
| 2008 | mean 26.4 w     | 5/5                     | 10                | 8 h      | mean 20.8 d | 0                     | 27        |
| 2003 | 26 w            | 1/1                     | 15                | 8 h      | 9 w         | 0                     | 28        |
| 2008 | 28 w            | 1/1                     | 10                | 8 h      | 10 d        | 0                     | 29        |
| 2006 | 24 and 30 w     | 2/2                     | 10                | 8 h      | 16/14 d     | 0                     | 30        |
| 2004 | 26 and 28 w     | 2/2                     | 10                | 12 h     | 20 d        | 50                    | 31        |

PT preterm, T term infant, w weeks, d days, y years,  
n.sp. not specified

**Table 2:** Treatment-related adverse events reported in >1% of 316 hospitalized children including 34 preterm infants <34 weeks of gestational age (randomized 2:1 to linezolid vs. vancomycin) infected with nosocomial multiresistant Gram-positive pathogens <sup>21</sup>

| Adverse Event    | Linezolid (n=213) | Vancomycin (n=99) | p-value |
|------------------|-------------------|-------------------|---------|
| Diarrhea         | 8 (3.8)*          | 6 (6.1)           | 0.3601  |
| Vomiting         | 4 (1.9)           | 1 (1.0)           | 0.5699  |
| Thrombocytopenia | 4 (1.9)           | 0 (0)             | 0.1700  |
| Loose stools     | 4 (1.9)           | 0 (0)             | 0.1700  |
| Rash             | 3 (1.4)           | 7 (7.1)           | 0.0082  |
| Nausea           | 3 (1.4)           | 0 (0)             | 0.2354  |
| Anemia           | 3 (1.4)           | 1 (1.0)           | 0.7710  |
| Eosinophilia     | 3 (1.4)           | 0 (0)             | 0.2354  |
| Oral moniliasis  | 2 (0.9)           | 4 (4.0)           | 0.0634  |
| Fever            | 1 (0.5)           | 3 (3.0)           | 0.0613  |
| Red man syndrome | 0 (0)             | 10 (10.1)         | <0.0001 |
| Pruritus         | 0 (0)             | 2 (2.0)           | 0.0374  |

\*numbers in parentheses, percent

## Figures

**Figure 1:** Comparison of linezolid pharmacokinetics in pediatric patients, adolescents and adults<sup>15</sup>.

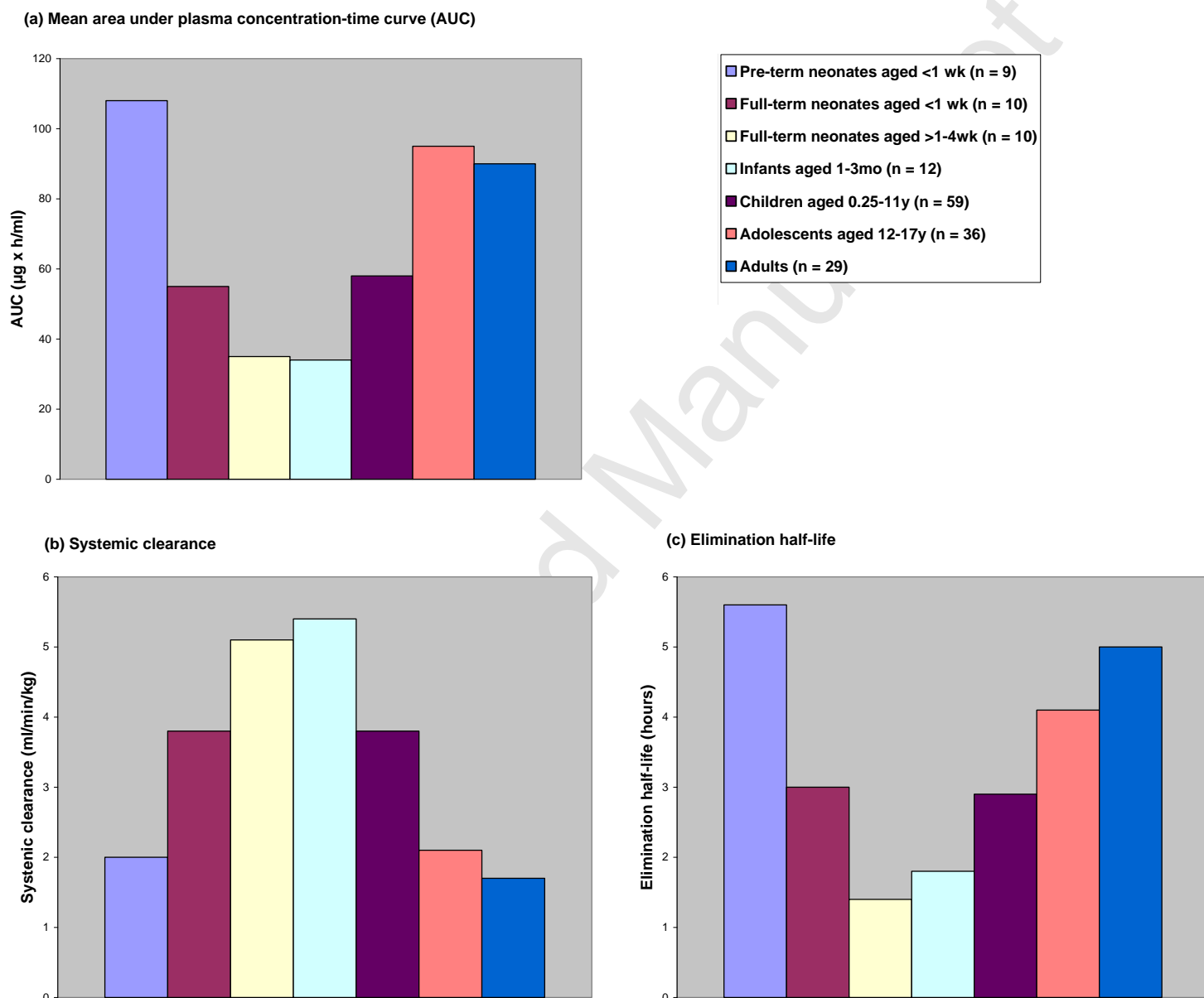


Fig.1: Pharmacokinetics of linezolid in pediatric patients, adolescents and adults. (a) Mean area under the plasma concentration-time curve (AUC), (b) systematic clearance, and (c) elimination half-life of single dose intravenous linezolid 10 mg/kg (maximum 600 mg) in (columns from left to right) pre-term [gestational age <34 weeks], full-term neonates aged below 1 week and between 1 and 4 weeks, infants, children, adolescent and adult volunteers.