

# Chloramphenicol Use and Susceptibility Patterns in Israel: A National Survey

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**ABSTRACT:** **Background:** Due to increasing antimicrobial resistance, there has been renewed interest in old drugs that have fallen into disuse because of toxic side effects. One such drug is chloramphenicol. Data on the use and susceptibility patterns to chloramphenicol in developed countries in recent years are limited.

**Objectives:** To assess the susceptibility of bacteria to chloramphenicol, and evaluate the use of chloramphenicol in Israeli hospitals as influenced by infectious disease specialists' attitudes with regard to its potential harms.

**Methods:** A national survey was conducted in all Israeli hospitals. Questionnaires were sent to the directors of infectious disease units and included items on chloramphenicol susceptibility in clinical isolates, use of chloramphenicol for the treatment of inpatients, local recommendations for use of chloramphenicol, and concerns regarding side effects.

**Results:** Chloramphenicol is used in 83.3% of hospitals, mostly for the treatment of aspiration pneumonia. While 22.2% of infectious disease unit directors believe that chloramphenicol should be avoided because of dangerous side effects, 88.9% believe there is a place for chloramphenicol in the treatment of patients in this era of increasing antibiotic resistance. Chloramphenicol susceptibility is routinely assessed in 44.4% of hospitals, with high susceptibility rates found among gram-positive, gram-negative and anaerobic bacteria.

**Conclusions:** In an era of increasing antibiotic resistance, many Israeli infectious disease unit directors believe that chloramphenicol has a role in the treatment of respiratory tract and other infections in hospitalized patients.

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**KEY WORDS:** chloramphenicol, susceptibility, toxicity, Israel

The emerging resistance to antibiotics worldwide has led to renewed interest in old drugs that have fallen into disuse because of toxic side effects. One such agent is chloramphenicol which was released for use in the United States in 1949, but

due to reports linking its use with the development of aplastic anemia it was rarely used as standard therapy in the developed world in the past few decades.

Chloramphenicol limits bacterial growth by binding to the 50S ribosomal subunit and inhibiting protein synthesis in the prokaryote [1]. It is active against a broad spectrum of organisms [2], has excellent tissue penetration [2], and is inexpensive. It is bacteriostatic against most pathogens but bactericidal against *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* [3]. In many developing countries chloramphenicol is still widely used to treat typhoid fever, anaerobic infections, bacterial meningitis in patients allergic to penicillin, brain abscesses, and rickettsial infections.

Resistance to chloramphenicol occurs through several mechanisms: reduced permeability or uptake, ribosomal mutation, and acetylation to an inactive derivative [4]. Despite reports a few decades ago of rapidly spreading resistance to chloramphenicol in *Salmonella typhi* and other bacterial pathogens [5], in recent years there seems to be a trend toward increased susceptibility which may be attributable to decreased use [6]. In *Salmonella typhi*, recent reports indicate the re-emergence of chloramphenicol-susceptible strains [6], with studies in the past year from India and Nepal finding > 90% susceptibility rates among *Salmonella typhi* and *paratyphi* isolates [7].

There are two types of bone marrow toxicity associated with chloramphenicol: reversible dose-related bone marrow suppression, and a rare idiosyncratic reaction of aplastic anemia that has an incidence of 1:24,500–40,800 [8]. While most cases of aplastic anemia followed the use of an oral preparation, some occurred even after local administration [9]. To date, there have been only 12 reports of irreversible aplastic anemia after intravenous chloramphenicol use [10].

The data on chloramphenicol use and susceptibility patterns in developed countries in recent years are limited. The aims of the present study were to assess the susceptibility of different bacterial isolates to chloramphenicol in hospitals across Israel, and to evaluate the use of chloramphenicol in Israeli hospitals as influenced by the concepts and beliefs of infectious disease (ID) specialists regarding its potential harms.

## SUBJECTS AND METHODS

We conducted a national survey in 2012 that included all Israeli hospitals. A questionnaire [Appendix 1] was sent to the directors of ID units in all 21 hospitals across Israel (with the exception of pediatric ID units). The questionnaire included the following items:

1. Does the microbiology laboratory in your hospital routinely assess susceptibility of clinical isolates to chloramphenicol, and if yes
  - a. What are the biological specimens and bacterial pathogens for which susceptibility is assessed?
  - b. What were the susceptibility rates found in your hospital in 2012?
2. Is chloramphenicol used for the treatment of patients in your hospital, and if yes, for what indications? (In Israel chloramphenicol for systemic use is only available as an intravenous preparation)
3. Does the ID unit in your hospital recommend in its local guidelines the use of chloramphenicol for the treatment of any infection, and if yes, for what indications?
4. Do you believe that chloramphenicol is a dangerous, harmful drug that should be avoided in the treatment of patients, and if yes, what are the potential side effects causing you to refrain from this treatment?
5. Do you believe that chloramphenicol treatment should be considered for specific indications, especially in this era of increasing antibiotic resistance?

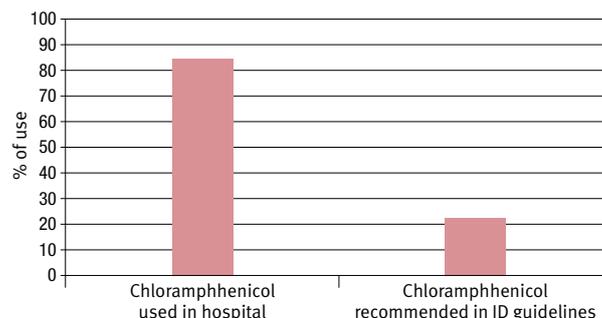
## RESULTS

Completed questionnaires were received from 18 of the 21 hospital ID units throughout Israel, representing 77.8% of all hospital beds in the country. All questionnaires were completely filled, with the exception of susceptibility rates to chloramphenicol which were reported by only eight ID units as detailed below.

Fifteen of the 18 ID units (83.3%) reported use of chloramphenicol in their hospital during 2012 [Figure 1]. The most common indication for treatment among those who reported using chloramphenicol was aspiration pneumonia (86.7%), followed by infected pressure ulcers (26.7%) and intra-abdominal infections (13.3%) [Figure 2]. Four hospital ID units (22.2%) reported that their local guidelines include a recommendation for chloramphenicol use: for the treatment of aspiration pneumonia (75%), intra-abdominal infections (25%) and nosocomial sepsis (25%).

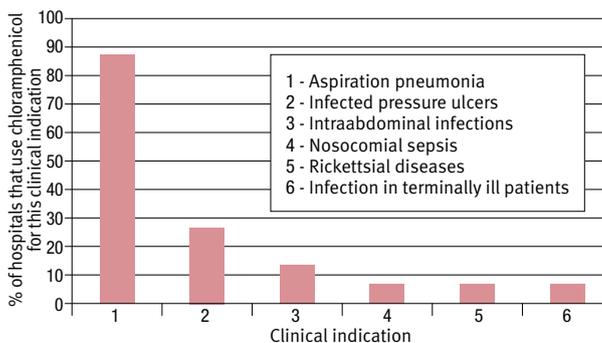
Overall, 4 of the 18 hospital ID unit directors (22.4%) believe that chloramphenicol is a drug with dangerous side effects that should not be used in clinical practice. The side effect cited most often was aplastic anemia (100%), followed by optic neuritis, hematologic malignancies, and hepatic toxicity. Fifteen ID directors (83.3%) held that the benefit achieved with chloram-

**Figure 1.** Percentage of infectious disease units that used chloramphenicol in 2012, and that include chloramphenicol use in their local guidelines



ID = infectious disease

**Figure 2.** Distribution of clinical indications for chloramphenicol use among hospital infectious disease units that reported chloramphenicol use in Israel (n=15)



phenicol treatment for certain indications exceeds the risk of side effects, especially for aspiration pneumonia (66.7%), intra-abdominal infections (20%), infected pressure ulcers (13.3%), infections caused by vancomycin-resistant enterococci (VRE) (6.7%), rickettsial infections during pregnancy (6.7%), and infections in terminally ill patients (6.7%). Sixteen of the ID unit directors (88.9%) contend there is a place for chloramphenicol in this era of increasing antibiotic resistance.

Of the 18 hospital microbiology laboratories, 8 (44.4%) routinely assess chloramphenicol susceptibility for different isolates. The specimens tested were blood (75%), sputum (75%), wounds (62.5%), abscesses (62.5%), intra-abdominal material (62.5%), cerebrospinal fluid (50%), gynecological samples (37.5%), conjunctival samples (25%), and stool (12.5%). Chloramphenicol susceptibility patterns of the specimens tested in each hospital stratified by pathogen are presented in Table 1.

## DISCUSSION

This study shows that up to 89% of ID unit directors in Israel believe there is a place for chloramphenicol in this era of

increasing antibiotic resistance, especially for the treatment of pneumonia in patients prone to aspiration, infected decubitus ulcers, and intra-abdominal infections. While there are no clinical data on the effectiveness of chloramphenicol in treating these conditions, most of the pathogens involved are susceptible to chloramphenicol and this drug obtains therapeutic levels in the lung, pleural and peritoneal cavities, skin and subcutaneous tissues. In a study conducted in a New York hospital in 2000, six patients with intra-abdominal infections caused by VRE that were susceptible to chloramphenicol were treated with this drug, resulting in eradication of VRE in all six cases, but the mortality rate remained high at 50% [11]. Our study also demonstrates 100% susceptibility of VRE to chloramphenicol. A recent systematic literature review of 113 studies on the in vitro activity of chloramphenicol against clinical ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp.) found high susceptibility rates among gram-positive bacteria. The authors concluded that though the risks related to chloramphenicol toxicity versus the benefits of this drug were not analyzed, and in light of the emerging problem of multi-drug-resistant pathogens, its role should be reassessed [12].

Despite our finding of the widespread use of chloramphenicol, only in 22% of Israeli hospitals did the ID unit's guidelines actually include a recommendation for chloramphenicol. This might be explained by the finding that 22% believe chloramphenicol to be a drug with dangerous side effects and should not be used in clinical practice. The side effect that was cited most often was aplastic anemia. There are two different forms of bone marrow suppression caused by chloramphenicol: dose-related reversible hematopoietic suppression and fatal idiosyncratic aplastic anemia found to occur in 1:24,500–40,800 courses of treatment [8]. Other commonly prescribed medications, such as the antipyretic dipyron, antithyroid drugs, and other antibiotic preparations, have been reported to cause irreversible bone marrow suppression, with an incidence as high as 1:1439 prescriptions for dipyron [13]. Most cases of aplastic anemia followed use of an oral chloramphenicol preparation, which was postulated to occur due to the absorption of by-products of the interaction between chloramphenicol and enteric bacteria [14]. In Israel, chloramphenicol for systemic use is available only as an intravenous preparation. To date, there have been only 12 reports of irreversible aplastic anemia after intravenous chloramphenicol use [10] and 7 reports following topical chloramphenicol use, though studies failed to detect chloramphenicol in the blood of patients treated with topical chloramphenicol.

We found that the susceptibility of clinical isolates to chloramphenicol was routinely assessed in 44% of hospitals. Susceptibility of Enterobacteriaceae ranged from 73% to 90%. Gram-negative blood isolates from children with febrile neu-

**Table 1.** Chloramphenicol susceptibility rates of specimens tested in each hospital\*, stratified by pathogen

| Pathogen type                     | Specimens tested and chloramphenicol susceptibility in the specific hospital |                         |                              |                                     | Overall weighted percentage of susceptible pathogens |
|-----------------------------------|--|-------------------------|------------------------------|-------------------------------------|--|
|                                   | Hospital no.**   | No. of specimens tested | No. of susceptible pathogens | Percentage of susceptible pathogens |  |
| Enterobacteriaceae                | 1  | 1115                    | 814                          | 73%                                 | 75%  |
|                                   | 2  | 897                     | 673                          | 75%                                 |  |
|                                   | 3  | 748                     | 561                          | 75%                                 |  |
|                                   | 4  | 85                      | 76                           | 90%                                 |  |
| Anaerobes                         | 1  | 173                     | 170                          | 98.5%                               | 98.5%  |
| <i>Streptococcus pneumoniae</i>   | 1  | 299                     | 299                          | 100%                                | 100%   |
|                                   | 3  | 137                     | 137                          | 100%                                |  |
|                                   | 5  | NAc                     | NA                           | 100%                                |  |
| Haemophilus species               | 5  | NA                      | NA                           | 100%                                | 100%   |
|                                   | 6  | 300                     | 300                          | 100%                                |  |
|                                   | 7  | NA                      | NA                           | 99.7%                               |  |
|                                   | 8  | NA                      | NA                           | 100%                                |  |
| VRE                               | 6  | NA                      | NA                           | 100%                                | 100%   |
| Enterococci                       | 2  | 1512                    | 1104                         | 73%                                 | 73%  |
| <i>Staphylococcus aureus</i>      | 1  | 336                     | 246                          | 73%                                 | 84.5%  |
|                                   | 2  | 1645                    | 1415                         | 86%                                 |  |
|                                   | 4  | 85                      | 85                           | 100%                                |  |
| Coagulase-negative Staphylococcus | 2  | 1512                    | 832                          | 55%                                 | 55%  |
| Shigella spp                      | 8  | NA                      | NA                           | 100%                                | 100%   |
| Salmonella spp                    | 8  | NA                      | NA                           | 100%                                | 100%   |
| Campylobacter spp                 | 8  | NA                      | NA                           | 100%                                | 100%   |

\* Of the 18 hospital microbiology laboratories that completed the questionnaire only 8 (44.4%) routinely assessed chloramphenicol susceptibility for different isolates

\*\* The eight hospitals that routinely assessed chloramphenicol susceptibility were each given a number ranging from 1 to 8

troponia in a hospital in Turkey demonstrated 88.9% sensitivity to chloramphenicol [15]. A recent study from our hospital found that 81.6% of 413 clinical isolates of Enterobacteriaceae were sensitive to chloramphenicol [16]. On the other hand, high resistance rates of Enterobacteriaceae have been reported in other studies: 46% of *E. coli* isolates from Ghana [17] and 24–100% of extended  $\beta$ -lactamase-producing *Klebsiella pneumoniae* isolates, according to a systematic review of 12 different studies [12]. One hospital in our study reported 98.5% susceptibility of anaerobes. Anaerobic bacteria, worldwide, have retained near 100% susceptibility to chloramphenicol [18]. Susceptibility of *S. pneumoniae* in blood and other isolates in our study was reported to be 100%. In a previous study, 99% of 1771 *S. pneumoniae* isolates in our medical center in 2008 were sensitive to chloramphenicol [16]. Studies from North America showed that 91% of *S. pneumoniae* isolates remained susceptible to chloramphenicol [19]. Sensitivity rates of *H. influenzae* and *H. parainfluenzae* in this study were 99.7–100%. Other studies also found high susceptibility rates, with 99.2% and 99.4% of *H. influenzae* isolates susceptible to chloramphenicol in Canada and the United States, respectively [20].

Susceptibility rates of *S. aureus* in our study were 73–100%. Methicillin-resistant *S. aureus* (MRSA) skin and soft tissue clinical isolates in a New York hospital in 2008 were 100% susceptible to chloramphenicol [21] and MRSA isolates in Buenos Aires demonstrated 97% susceptibility [22]. In our study, one center reported 72% susceptibility of all enterococcal isolates, and another found susceptibility rates of 100% of VRE to chloramphenicol. A national surveillance program conducted in Canada during the decade 1999–2009 found that VRE blood isolates collected across the country were 100% susceptible to chloramphenicol [23]. Susceptibility rates of 100% of Shigella, Salmonella and Campylobacter species were reported from one hospital in our study. Chloramphenicol resistance in *Salmonella enterica* gastroenteritis strains in Botswana decreased from 56% to 6% from 2003 to 2008 [24], though 53% resistance was found among Shigella spp. isolates from Ethiopia [25].

Our study has several limitations. One major limitation is the small number of hospitals that reported sensitivity rates to chloramphenicol for each bacterial pathogen, mostly because chloramphenicol is not routinely found in the antibiotic susceptibility dispensers used in Israeli microbiology laboratories; in each hospital it is assessed for different isolates at the discrepancy of the lab. Also, some reported only the percent of susceptible pathogens and not the absolute numbers that were tested. Even so, we received a report from each hospital of all the isolates tested for chloramphenicol susceptibility during 2012, amounting to hundreds and even thousands of isolates. Also, our data address only in vitro susceptibility and not clinical efficacy of chloramphenicol. Another limitation is that we sent the questionnaire to the directors of all Israeli ID units only (resulting in only 18 filled questionnaires) and not to all ID specialists or to other medical practitioners, which might have provided a wider view of attitudes to chloramphenicol use.

In conclusion, in an era of increasing antibiotic resistance and in view of relatively high susceptibility rates, many directors of ID units in Israel believe chloramphenicol might have a role in the treatment of respiratory tract and other infections in hospitalized patients. More data on susceptibility rates of bacterial isolates to this drug from developed countries and more recent data on toxicity versus efficacy are required to reassess the therapeutic use of this drug.

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**Appendix 1. National survey of chloramphenicol use among infectious disease units in Israel**

**1. Does the microbiology lab in your hospital routinely assess susceptibility of clinical isolates to chloramphenicol?**  Yes  No

**1.1 If yes, what isolates are tested for chloramphenicol susceptibility?**

- 1.1.1 Blood  Yes  No
- 1.1.2 Sputum  Yes  No
- 1.1.3 CSF  Yes  No
- 1.1.4 Wounds  Yes  No
- 1.1.5 Abscesses  Yes  No
- 1.1.6 Intra-abdominal samples  Yes  No
- 1.1.7 Gynecological samples  Yes  No
- 1.1.8 Other sample: \_\_\_\_\_  Yes  No
- 1.1.9 Other sample: \_\_\_\_\_  Yes  No
- 1.1.10 Other sample: \_\_\_\_\_  Yes  No

**1.2 If yes, what pathogens are tested for chloramphenicol susceptibility?**

- 1.2.1 Enterobacteriaceae  Yes  No
- 1.2.2 Anaerobes  Yes  No
- 1.2.3 *Strep. Pneumoniae*  Yes  No
- 1.2.4 *Staph. Aureus*  Yes  No
- 1.2.5 Other pathogen: \_\_\_\_\_  Yes  No
- 1.2.6 Other pathogen: \_\_\_\_\_  Yes  No
- 1.2.7 Other pathogen: \_\_\_\_\_  Yes  No

**1.3 If yes, what are the susceptibility rates to chloramphenicol in blood isolates?**

- 1.3.1 Not tested/not known
- 1.3.2 Enterobacteriaceae Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.3.3 Anaerobes Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.3.4 *Strep. pneumoniae* Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.3.5 *Staph. aureus* Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.3.6 Other pathogen: \_\_\_\_\_ Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.3.7 Other pathogen: \_\_\_\_\_ Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.3.8 Other pathogen: \_\_\_\_\_ Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_

**1.4 If yes, what are the susceptibility rates to chloramphenicol in other isolates?**

- 1.4.1 Not tested/ Not known/ Other culture
- 1.4.2 Enterobacteriaceae Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.4.3 Anaerobes Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.4.4 *Strep. pneumoniae* Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.4.4 *Staph. aureus* Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.4.5 Other pathogen: \_\_\_\_\_ Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.4.6 Other pathogen: \_\_\_\_\_ Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_
- 1.4.7 Other pathogen: \_\_\_\_\_ Susceptibility % \_\_\_\_\_ Year \_\_\_\_\_

**2. Is chloramphenicol used in your hospital?**  Yes  No

**2.1 If yes, for what indications?**

- 2.1.1 Aspiration pneumonia  Yes  No
- 2.1.2 Intra-abdominal infections  Yes  No
- 2.1.3 Other Infection: \_\_\_\_\_  Yes  No
- 2.1.4 Other Infection: \_\_\_\_\_  Yes  No

**3. Does the ID unit in your hospital recommend in its guidelines the use of chloramphenicol for the treatment of various infections?**  Yes  No

**3.1 If yes, for what infections?**

- 3.1.1 Aspiration pneumonia  Yes  No
- 3.1.2 Intra-abdominal infections  Yes  No
- 3.1.3 Other Infection: \_\_\_\_\_  Yes  No
- 3.1.4 Other Infection: \_\_\_\_\_  Yes  No

**4. In your opinion, is chloramphenicol a drug with dangerous side effects that should be avoided in treatment of patients?**  Yes  No

**4.1 If yes, what are the potential side effects causing you to refrain from this treatment?**

- 4.1.1 Aplastic anemia  Yes  No
- 4.1.2 Optic neuritis  Yes  No
- 4.1.3 Hematologic malignancies  Yes  No
- 4.1.4 Hepatic toxicity  Yes  No
- 4.1.5 Other: \_\_\_\_\_  Yes  No
- 4.1.6 Other: \_\_\_\_\_  Yes  No

**5. In your opinion, does the efficacy of chloramphenicol treatment for certain infections exceed the potentially dangerous side effects?**  Yes  No

**5.1 If yes, for what infections?**

- 5.1.1 Aspiration pneumonia  Yes  No
- 5.1.2 Intra-abdominal infections  Yes  No
- 5.1.3 Other Infection: \_\_\_\_\_  Yes  No
- 5.1.4 Other Infection: \_\_\_\_\_  Yes  No

**5.2 If No, please elaborate:** \_\_\_\_\_

**6. Do you believe that chloramphenicol has a role in treating infections in hospitalized patients in this era of increasing antibiotic resistance?**

Yes  No

Please elaborate: \_\_\_\_\_