Durg Corner

Lincomycin : A review and meta-analysis of its efficacy and tolerance in common infections encountered in clinical practice

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Lincomycin, the first antibiotic of the Lincosamide class, has been studied and used in several common outpatient and hospital-based infections, in both its oral and injectable forms. The main ones among these are Ear Nose Throat (ENT) and Respiratory Tract Infections (RTI), skin and Soft Tissue Infections (SSTI) including surgical wound infections, bone and joint Infections (osteomyelitis and septic arthritis), and oro-dental infections. Its spectrum of action covers Gram-positive bacteria mainly Staphylococcus, Streptococcus (pyogenes, viridans, pneumoniae), C diphtheriae, and Anaerobic bacteria including Clostridium Propionibacterium. Though there are several clinical and microbiological studies which have evaluated the efficacy and tolerance of Lincomycin in various common infections seen in clinical practice, the evidence present has not been widely reviewed, or propagated in the last few decades. Studies and data associated with the bacteriological sensitivity, clinical usage and benefit, adverse effects and place in infectious disease therapy has been reviewed and analyzed in detail here. Lincomycin can be a useful part of the currently available antibiotic armamentarium. More real-world and clinical studies, as well as study of microbiological sensitivity patterns should be further initiated for improving insights on the place of antibiotic.

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Lincomycin is the first antibiotic from the Lincosamide class, isolated from the actinomycete Streptomyces lincolnensis in 1964. It acts by inhibiting protein synthesis in susceptible bacteria by binding to the 50 S subunits of bacterial ribosomes and preventing formation of the peptide bond during transcription[1-3]. Though considered bacteriostatic, it is bactericidal against susceptible bacteria and also when used in high concentrations. Its spectrum of action covers Gram-positive bacteria mainly Staphylococcus, Streptococcus (pyogenes, viridans, pneumoniae), C diphtheriae, and Anaerobic bacteria including Clostridium (tetani and perfringens) and Propionibacterium.

Lincomycin has been used in bacterial infections of the respiratory system, skin and soft tissue including wounds, bone and joint, and oro-dental infections and is especially a useful option against Penicillinase producing and Erythromycin resistant strains. Lincomycin has limited activity against Enterococcus faecalis and no activity against Gram-negative bacteria like Enterobacteriaceae group, Neisseria and Hemophilus. Lincomycin is to be used in cases proven or strongly suspected to be caused by susceptible bacteria based on information from culture-sensitivity or local epidemiology and susceptibility patterns[1-3].

Oral bioavailability of Lincomycin is 25-50% in fasting state, and is significantly reduced by meals. Peak plasma concentrations of 2-5ug/ml is achieved in 2-4 hours and maintained for 6-8 hours. Intramuscular administration of a single dose of 600 mg of Lincomycin produces average peak plasma levels within an hour (usually 15-20 minutes) in the range of 11-12µg/mL with therapeutic levels maintained for 17 to 20 hours for most susceptible Gram-positive organisms. If given as an IV infusion, Lincomycin attains up to 15-16ug/ml plasma concentrations maintained over 14 hours.

Peak bone concentrations are usually attained in about 2-3 hours at a level of 2-2.5ug/ml. Excretion is mostly through bile, with 10-15% excretion through urine[2,4,5].

Microbiological spectrum and effectiveness :

One of the recognized ways of reducing resistance is not using a broad-spectrum antibiotic, when a narrow spectrum antibiotic effective against the causative organism is present. Lincomycin is one of the most sensitive and effective options for Group A Streptococci infections (MICs 0.12-1ug/ml) which show high resistance to Penicillin[6]. Lincomycin is effective against Staphylococcus aureus (and S albus) at

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minimum inhibitory concentrations (MICs) of 0.7-1.55 ug/ml and compares favorably to other antibiotics at an MIC of 2ug/ml[7]. Studies have shown concentrations of 2.5-5.0 ug/ml and 0.67-3.9 ug/ml after the 1000mg and 500mg Lincomycin oral dosages, and 3.5-10 ug/ml after 600mg intramuscular dose (IM), with a >95% sensitivity to Staphylococcus aureus (30ug discs) as compared to <20% for Penicillin[8].

In a study, Lincomycin showed 98.7% sensitivity to hospital based Staphylococcal strains (with the resistant strains being phage typed as Atypical Group III). Lincomycin also showed 100% sensitivity to hospital isolated strains of Streptococcus pyogenes, Streptococcus viridans, Pneumococcus, other hemolytic Streptococci and Clostridium perfringens, with 98% sensitivity to Enterococcus strains[9]. A study from Uganda showed that 90%, 49%, 10% and 18% Staphylococcal resistance was seen to Penicillin, Streptomycin, Oxytetracycline and Cloxacillin respectively with none seen for Lincomycin[10] Penicillin G and Erythromycin resistant S aureus is frequently not resistant to Lincomycin[5]. Against Clostridium species and C diphtheriae, Lincomycin has shown MICs in the range of 0.3-1 ug/ml[3]. Apart from being effective against Penicillinase resistant Staphylococci, Lincomycin is also effective against Hemophilus vaginalis[11].

Lincomycin shows good penetration into pleural and cerebrospinal fluid[12,13]. Lincomycin has very good bone penetration with 75% of serum concentration in spongy bone and 15% in compact bone[14].

The plasma, bone, hip capsule, synovial and drain fluid concentrations of Lincomycin were maintained above MIC of Penicillinase producing Staphylococcus[15]. Lincomycin is comparable to Clindamycin in attaining MIC in synovial fluid within an hour in patients of Rheumatoid Arthritis[16]. Lincomycin has shown good clinical response in treating acute and chronic osteomyelitis, and septic arthritis and would appear to be one of the drugs of choice for acute or chronic Staphylococcal bone or joint disease, as well as an effective option in post hip replacement surgery[17]. It can be given for prolonged periods due to its low toxicity and high bone penetration (achieving consistent MICs of 0.25-2 ug/ml).[18]

Lincomycin and Clindamycin :

Clindamycin was developed from Lincomycin 2 years later in 1966 by inversion of chirality and replacing 7 hydroxy group with a chlorine atom[19]. Clindamycin was ascertained to have better oral absorption (which can lower gastrointestinal side effects like diarrhea) and higher in vitro sensitivity to susceptible organisms[20]. However, both antibiotics are equally potent in blocking their ribosomal target site, and show similar MICs and clinical effectiveness against susceptible organisms[21-23].

Lincomycin was nonetheless widely substituted in clinical use for Gram-positive and Anaerobic infections, by Clindamycin, till the association of Clindamycin with Pseudomembranous colitis due to C difficile in 1973. Thereafter the usage of Clindamycin declined but emerged again once the etiology and management of Pseudomembranous colitis had been understood and advocated[24].

Lincomycin showed less disturbance of faecal flora and Enterobacteriaceae counts as compared to Clindamycin. (48-50% *versus* 60-75%)[25]. Though both drugs may be associated with neuromuscular blocking actions in high doses, Lincomycin does not increase acetylcholine release, does not have an anesthetic action and has a 5 times less neuromuscular blocking effect due to an effect on the muscle, than Clindamycin[26].

Due to the quick switch to Clindamycin within 2 years of the availability of Lincomycin, the robust clinical data of Lincomycin in various common clinical outpatient and hospital infections has not been widely reviewed, analyzed or propagated in the last few decades. Since Lincomycin represents an important member of the Lincosamide group with potential to effectively treat Gram-positive and Anaerobic infections, it is important to review its clinical efficacy and tolerance, for its befitting place in the currently available antibiotic armamentarium.

Lincomycin Clinical Efficacy and Usage :

Lincomycin has been studied in several common outpatient and hospital-based infections. The main ones among these are Ear Nose Throat (ENT) and Respiratory Tract Infections (RTI), Skin And Soft Tissue Infections (SSTI) including surgical wound infections, bone and joint Infections (osteomyelitis and septic arthritis), and oro-dental infections. Databases were searched for clinical studies of Lincomycin and 56 studies were reviewed and analyzed. Individual case studies, studies with ill- defined outcome parameters and improper methodology were not taken into consideration, and in all 21 studies were included for meta-analysis (Fig 1).

In all these studies, Lincomycin has been dosed in accordance to its recommendation[2-4]. The oral dose (available as 250/500 mg capsules) was given as 1-2 g/day in divided doses 2 hours before or after meals, for out-patient treatment or step-down therapy. For infections requiring hospitalization or related to surgery,

the injectable form was used, as 600mg Intramuscularly (IM) or by Intravenous (IV) infusion given 12-24 hourly depending on severity of infection. Doses through IV infusions maybe stepped up to 8 g/day for life threatening infections. Dosage in children is 30- 60mg/kg/day and 10-20mg/kg/day for oral and injectable forms. Serum drug levels should be monitored (especially if high doses are being used) in liver dysfunction, and dose reduced by 25% or frequency decreased in patients with renal dysfunction. Duration of treatment is usually 3-7 days extending to 10 days for group A, beta-hemolytic Streptococci (GABS) infections in children. Long term treatment over a few months maybe required for bone and joint infections.

Respiratory Tract Infections :

ENT and URTI :

Lincomycin has shown efficacy in the management of ENT infections including acute upper respiratory tract infections (URTI- tonsillitis, pharyngitis, sinusitis), acute otitis media (AOM) along with pneumonia (lobar and bronchopneumonia). It has also shown efficacy in treating group A Streptococcal infection in children.

In a recent Indian study of 40 adult patients with tonsillitis or sinusitis, oral Lincomycin 500mg and Cefpodoxime 200mg dosed twice daily for 5 days, were studied. At the end of the study, 67.9% and 52.3% achieved complete symptomatic relief with Lincomycin and Cefpodoxime respectively[27]. Complete relief from fever and pharyngeal congestion was achieved in 93.7% and 87.5%, and 100% and 66.7% in the Lincomycin and Cefpodoxime groups respectively. In another study of 22 out- patients with predominantly Gram-positive ENT infections, there was a 100% good response[28].

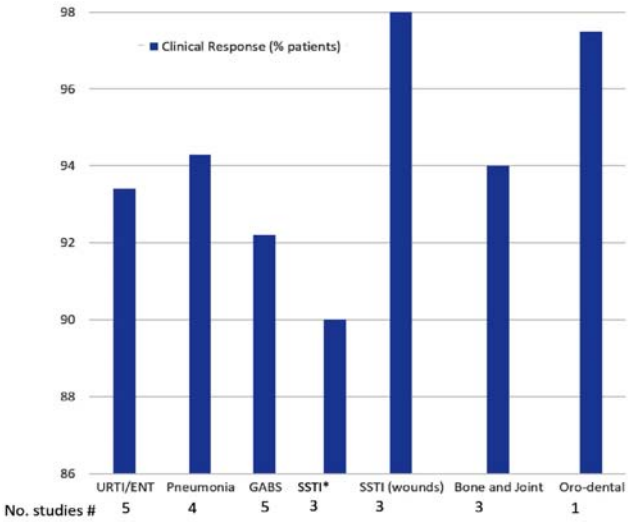

Fig 1 — Clinical Response Rates for Lincomycin in Infections caused by Susceptible bacteria (Meta- analysis)

Abbreviations : URTI- Upper Respiratory Tract Infections; ENT- Ear Nose Throat; GABS- Group A Beta-hemolytic Streptococci, SSTI- Skin and Soft Tissue Infection

*SSTIs include bacterial/pustular dermatosis, pyodermas, folliculitis, furuncles and impetigo

#URTI/ENT[27-31], Pneumonia[33-36], GABS[37-40], SSTI[41,43,44], SSTI (wounds)[41,44, 45], Bone and Joint[46-48], Oro-dental[50]

In another study on ENT infections in 88 patients, 53/58 (91.3%) and 21/30 (70%) of acute and chronic infections showed symptomatic relief in a week. (25/25 acute sinusitis, 12/14 chronic sinusitis, 9/12 AOM, 6/12 chronic otitis media, 10/10 in tonsillopharyngitis)[29]. Resistant Gram- negative strains were seen in 50% of treatment failures, while longer treatment was recommended in chronic cases. Transient diarrhea was seen in 5 patients with no treatment cessation needed.

In another similar study of 75 patients with acute URTI and AOM, clinical cure in 68/75 (90.6%) was achieved[30].

In a study of 60 patients (including Diphtheria 24, Scarlet fever 16, Pneumococcal pneumonia 13 and bacterial pharyngitis 7), 96.7% showed a good to excellent outcome, with no significant side effects.[31] In a study on Asthma patients with Upper Respiratory Tract Infections (URTI), excellent or good outcome was seen in 36/51 (70.6%) who mainly had Gram-positive infections with Staphylococci, Streptococci or Pneumococci[32].

Pneumonia :

In 2 different studies of 43 and 42 evaluable patients with Pneumococcal pneumonia, 42/43 (97.6%) and 39/42 (92.8%) patients treated with Lincomycin showed good to excellent response[33,34]. 1 mortality occurred due to Klabsiella superinfection in the first study, and no toxicity or impaired tolerance to Lincomycin was seen in both these studies. In a multi-organism pneumonia study with 30 patients (28 hospitalized, 2 OPD; 1 lung abscess, 18 lobar and 11 broncho-pneumonia), 90% were cured, 6.6% showed improvement, 29 showed radiological improvement or cure, and the lung abscess resolved completely with Lincomycin[35].

In a study from Mumbai with patients of multi-organism lobar pneumonia given Lincomycin, clinical response was good in 22/25 (88%) patients, with normal temperature attained in 2-3 days and disappearance of cough and chest pain in 5-7 days[36]. Radiological improvement occurred in about 10 days. The organisms cultured included haemolytic Streptococci in 9, Streptococcus pneumoniae in 5, Staphylococcus albus in 5, Klebsiella pneumoniae in 4, Proteus vulgaris in 2 and Escherichia coli in 2 patients with more than one pathogen isolated in 6

patients. Transient diarrhea not needing stoppage of treatment was seen in only 1 patient.

Pediatric GABS infections :

There are 4 large clinical studies in children with Group A Streptococci pharyngitis and tonsillitis. In a study of 870 children, negative cultures were seen in one week 93% *versus* 89% for Lincomycin and Penicillin respectively[37]. Transient and inconsequential diarrhea was seen in 9%. In the second study of 525 patients, cure rate of 92.1% was seen with Lincomycin versus 86.1% for Penicillin[38]. Significant improvement in 12-24 hours along with negative throat cultures on the 3rd day was seen in all but 1 and 5 in Lincomycin and Penicillin group respectively. Majority returned to full activity by 3rd day. Clinical recurrence was 4.8% *versus* 7.5% for Lincomycin *versus* Penicillin.

In another study with 303 children, comparing Lincomycin with Ampicillin and Penicillin, the cure rates were 82% *versus* 71.3% *versus* 70.6% (Lincomycin *versus* Ampicillin *versus* Penicillin) with Lincomycin showing lowest relapse rate and 0% carrier rate at 4 weeks (*versus* 7% and 12.7%)[39]. Improvement within 24 hours and fever below 100 deg F by day 2 was seen in 95% of the patients. A study comparing with Clarithromycin showed clinical cure at 12-14 days in 88, 80, 82%, microbiological eradication in 98, 91, 96% and 3-month recurrence in 0, 3, 0% with Lincomycin, Penicillin and Clarithromycin respectively[40].

Skin and Soft Tissue Infections :

Skin infections are commonly caused by Gram-positive and anaerobic bacteria like Staphylococcus, Streptococcus and Propionibacterium, therefore Lincomycin can have a valuable place in SSTI management.

In a recent Indian study, 30 patients with SSTIs were evaluated for response to Lincomycin 500mg oral capsules given twice/thrice daily. Complete relief of clinical signs and symptoms by day 14 was overall around 80% as follows: cellulitis 60%, folliculitis 85.7%, furuncles 66.7%, carbuncles 50%, oozing wounds 90.9%, and open wounds/surgical site infections 100%[41]. A patient each reported urticaria and diarrhea as adverse effect which subsided spontaneously. Another smaller study with 14 patients showed improvements within 24 hours and average healing time in eczematous dermatitis and folliculitis of 3-5 days, furuncles and carbuncles 7-13 days, cellulitis, lymphangitis, and lymphadenitis 3-7 days with Lincomycin[42]. One patient of cystic acne achieved first time clearance in 15 years which was maintained for 9 months on Lincomycin 500mg OD.

A large study in bacterial dermatosis with 315 patients was done with excellent or satisfactory response in 271/315 (86%)[43]. The study included Impetigo, furunculosis, pustular dermatitis, pustular psoriasis, cystic acne and pyodermas. High rates of clearance of cystic acne were seen 140/171 (82%) with a 100% response in Impetigo and furunculosis, and >95% response in pustular dermatosis. Transient diarrhea not needing discontinuation, was seen when high dose, or prolonged therapy was used. Another study of 30 patients with Staphylococcal (2/3rds) and Streptococcal soft tissue infections (19 abscesses, 5 cellulitis, 5 infected wounds, and 1 phebitis) showed a satisfactory clinical response in all cases[44]. A small study of surgical site/wound infections showed marked improvement with excellent response in 25/27 (92.6%) patients[45]. Majority of isolates were of Staphylococcal and the 3 cases being Streptococcal on microbiological testing. A study of 150 patients with Staphylococcal acute abscesses, similar rates of healing were seen with Lincomycin and Clindamycin when given for 4 days post incision and drainage[23].

Bone and Joint Infections :

Lincomycin achieves good levels in Bone and Joint, and can be an effective option in cases of Osteomyelitis due to the ability to give it for prolonged periods with low toxicity, high efficacy and low recurrent rates[18]. In a study of 25 Osteomyelitis cases treated with Lincomycin, no recurrence was seen in 24/25 (96%) for 2 years (recurred case was given inadequate dosage)[46]. In 50 cases of Chronic Osteomyelitis, Lincomycin along with removal of dead and ischemic cells improved healing rates.[47] Of the 50 patients, 47 healed (94%) and 41 remained healed for an observation period lasting from nine months to three years, and ten months. In a study conducted over a 5-year period, 121 patients with Acute Hematogenous Osteomyelitis or Chronic Osteomyelitis were evaluated.[48] Lincomycin produced cure in 113/121 (93.4%).

In a study of 62 patients with Post-operative Osteomyelitis (89% lower limb fractures with 54% closed fractures), Staphylococcal strains were isolated in 80% cases with 68% being Penicillin resistant. Results with Lincomycin were good in 74%, and fair in 8%, with Lincomycin resistance seen in 3 patients, and an amputation rate of 13%[49].

Oro-dental infections :

Lincomycin has been seen to be effective in oro-dental and circumoral infections caused by

Staphylococcus and Anaerobes[50]. A recent Indian clinical study evaluated 42 patients with oro- dental infections by administering oral Lincomycin 500 mg for 5 days. At end of treatment 100% of gingivitis patients and 96.8% of periodontitis patients achieved complete relief from signs and symptoms of pain/ tenderness, bleeding, halitosis, sensitivity to heat/cold, tooth mobility, redness, presence of exudates or evidence of bone destruction. Relief by day 2 was seen in 85.7% and 88.4% patients in the 2 groups. No adverse events were seen in the study.

Common infections in Clinical Practice :

Clinical studies with Lincomycin have been performed to see its efficacy, tolerance and use in general and common out-patient and in-patient clinical practice.

In a study of 18 patients (50% osteomyelitis, enteritis, arthritis and SSTI), where the cultured organism was predominantly Staphylococcus aureus, culture negativity was achieved in an average of 10 days with Lincomycin in most patients[7]. In another study of 70 hospitalized patients with Staphylococcal and Streptococcal infections treated with Lincomycin, total recovery rate of 78.5% (55/70) with complete recovery in 16/22 patients with Staphylococcal infections, 9/14 with pneumonia, 15/17 with acute exacerbations of bronchitis and 2 patients with other bacterial infections was seen[52]. The study concluded that the place of Lincomycin in therapeutics seems to be principally in the treatment of chronic osteomyelitis, in patients allergic to the Penicillins, and in the treatment of staphylococcal respiratory and other infections for which Penicillin is usually employed. Only 4 patients had mild-transient diarrhea not requiring therapy cessation.

In a group of infections comprising of osteomyelitis, septic arthritis, bronchopneumonia and SSTI, in 22 patients, 19/24 (79.2%) showed clinical cure and 14/ 24 showed bacteriological cure[53]. Only one patient had mild-transient diarrhea not requiring therapy cessation. Another study with 65 patients of osteomyelitis, septic arthritis, pneumococcal meningitis, endocarditis, and septicemia, cure rates were as follows: Bone Joint Infections 31/52 cured, 12 satisfactorily responded, 8 failures (all chronic infections), 1 relapsed; Pneumococcal meningitis 3/3 responded; Septicemia including endocarditis 8/10 responded well.[54] Overall response rate was satisfactory/good 54/65 (83%) with 8 cases of mild-transient diarrhea not requiring therapy cessation.

In a general practice study, good clinical response with Lincomycin was seen in 83/96 (86.5%) patients (Pneumonia 36/42, Pharyngotonsillitis 12/13, Osteomyelitis 17/17 and Wound-Soft tissue infections 12/13).[55] Adverse effects included 6 cases of diarrhea and 1 mildly pruritic drug eruption, all showing spontaneous resolution. Similar good to excellent response with Lincomycin was seen in 43/56 or 76.8% patients (pharyngotonsillitis 12/13, sinusitis 7/10, carbuncle/furuncle 12/14, otitis media 5/5, pustular acne 3/4, miscellaneous infections 5/6) in another study[56]. Though troublesome diarrhea was seen in 5 patients, it did not interrupt treatment. A third study also showed overall 47/55 (85.4%) showed good therapeutic result in 47/55 patients (16/18 pneumonia, 9/10 tonsillopharyngitis, 1/1 lung abscess, osteomyelitis 9/9)[57]. A study done in 37 patients with pharyngotonsillitis, bronchitis, sinusitis, osteomyelitis, SSTI and wound Infections showed good response in 36 (97.3%) patients with rapid response <24 hours seen in some cases[58].

A pediatric clinical practice study performed, showed cure achieved in all 295 children with mean duration of therapy of 15 days with injectable Lincomycin[59]. The infections included mainly skin and soft tissue, and bone and joint infections. No significant adverse effects were seen.

Discussion

Lincomycin has been seen to be of benefit in several clinical studies where infections were due to susceptible bacteria like Gram-positive and Anaerobic organisms. It has been found efficacious in acute upper respiratory tract infections and ENT infections including tonsillitis, pharyngitis, sinusitis and AOM, as well as Pneumococcal pneumonia and pediatric Streptococcal infections[27-40]. Lincomycin can be an effective option in RTIs when the susceptibility local trends and epidemiology are known, and when culture data is available. Among SSTI, wound infections, including surgical ones, display a high response to Lincomycin[41-45]. The response has been effective in bacterial dermatosis like folliculitis, furunculosis, impetigo and pyodermas, however deeper infections like cellulitis, and carbuncles may need more prolonged or injectable treatment. Lincomycin along with incision-drainage gives effective results in abscesses[23]. Lincomycin, given as prolonged maintenance oral therapy can be an asset for nodulo-cystic acne[43]. For mild-moderate acne, now Lincomycin in also available in a 2% topical form[60].

In acute bone and joint infections, like osteomyelitis and septic arthritis, Lincomycin has shown good results when given in appropriate prolonged regimens to maintain minimal relapse rates[18,46-49]. One dental

study has shown high response rates in gingivitis and periodontitis which are predominantly Staphylococcal and Anaerobic infections. The study also showed effectiveness of Lincomycin in managing procedure related infections[50]. Lincomycin has shown to have a valuable place in several common out-patient and in-patient infections encountered in general clinical practice. However often such infections may display mixed microbiology including Gram-positive, negative and Anaerobic bacteria. Combining Lincomycin with Aminoglycoside antibiotics can be an effective strategy in managing such infections in hospitalized patients[61].

Lincomycin has shown acceptable tolerance in the reviewed study. While diarrhea is the predominant side effect seen in up to 10% cases, it was transient, seen more with higher doses, and also did not necessitate cessation of therapy. Though cases with Lincosamides of Pseudomembranous colitis have been reported in literature, none were seen in the studies of Lincomycin reviewed[62]. No other significant adverse effects have been seen with Lincomycin.

Conclusion

Lincomycin when appropriately used can be a valuable part of the current antibiotic armamentarium. Based on the data of efficacy and tolerance reviewed, more recent clinical and real-world studies are warranted for Lincomycin (oral/injectable) used both as monotherapy in known susceptible infections, and as combination empirical therapy in common infections. Recently Lincomycin has shown efficacy and become available as a 2% topical formulation for acne and bacterial skin infections[62]. Also, there should be more research in to inducible and cross resistance patterns of Lincomycin along with other antibiotics.

Conflict of Interest : The authors are medical consultants to Wallace Pharmaceuticals, India.

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