Drug Corner

Lincomycin in Skin and Soft Tissue Infections and Upper Respiratory Tract Infections

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Objective : To review the literature for evidence of the efficacy of lincomycin in skin and soft tissue infections (SSIs) and in Upper respiratory tract infections (URTIs), and the current scope of lincomycin use in these infections.

Methodology : Computerized searches of the PubMed and Google scholar database were performed to identify primary and review articles about the therapeutic use of lincomycin between 2000 and 2020. The keywords used during the search were 'lincomycin and skin infection', 'lincomycin and soft tissues infection', lincomycin and urinary tract infection', and 'lincomycin review'.

Data analysis and conclusions : The efficacy of lincomycin in skin and soft tissue infections as well as in Upper Respiratory Tract Infections (URTIs)has been proven in many studies. Perhaps, local variations in antibiotic resistance of organisms lead to these variations. Most studies showed Staphylococcus aureus (S. aureus) accounting for 35-50% of infections.Lincomycin still seems to be an effective therapy in conditions like periodontitis, perioperative preventive and curative therapy, and certain skin conditions like folliculitis as well as topical application for acne. Lincomycin might still also be effective in cases of URTI not responding to the standard lines of treatment. It also seems to have an important role in Group A Beta-hemolytic Streptococcal Pharyngo-Tonsillitis.

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Key words **: Lincomycin, Soft Tissue Infections.**

Lincomycin is obtained from the actinomyces Streptomyces lincolnensis. Chemically, it is a 6,8-dideoxy-6-aminooctose lincosamine[1]. It was isolated in 1962 and was the first lincosamide to be used in clinical practice. Lincomycin has an antibacterial effect on Gram-positivemicroorganisms (staphylococci, streptococci, pneumococci, diphtheria bacillus,and clostridia) and is usually reserved for serious bacterial infections like sepsis, osteomyelitis,septic endocarditis, pneumonia, pulmonary abscess, infected wounds, andpurulent meningitis, that areresistant to penicillin and other antibiotics[2]. Most Gram-positive cocci including staphylococci, pneumococci, and most streptococci [except S (faecalis)] are usually sensitive to lincomycin but Neisseriae and H influenzae are resistant. Other organisms that are sensitive to lincomycin include Mycoplasma hominis and M. pneumoniae (but not T strains) and Bacteroides spp[3,5].

Lincomycin acts by inhibiting protein synthesis at ribosomal binding sites. It is well absorbed after oral or intramuscular administration and is widely distributed in the body. It is also detected in cord blood and milk, although little gets into the normal cerebrospinal fluid. Due to its high concentration in the bone, it is often used in the management of acute staphylococcal osteomyelitis. Following oral dosing,it rapidly reaches peak levels in the serum and the minimum inhibitory concentration (MIC) of sensitive organisms is promptly exceeded; hence, a 4 to 6 hourly dosage regimen is recommended. Intramuscular administration of a single dose of 600 mg of lincomycin produces average peak serum concentrations of 11.6 mcg/mL at 60 minutes. The therapeutic concentration is maintained for 17 to 20 hours for most susceptible gram-positive organisms. A two-hour intravenous infusion of 600 mg of lincomycin achieves average peak serum concentrations of 15.9 mcg/mL and maintains therapeutic concentrations for 14 hours for most susceptible gram-positive organisms[4,6].

The excretion of lincomycin is mainly through the bile and faecal route. A small proportion of lincomycin (9% in 24 hours) is excreted by the kidneys; however, the serum concentrations of lincomycin can be very high in patients with renal failure[3]. The biological half-life after intramuscular or intravenous administration is 5.4 ± 1.0 hours. In patients with hepatic impairment, serum half-life might be twice of that in patients with normal hepatic function[6].

This paper reviews the literature for evidence of the efficacy of lincomycin in skin and soft tissue infections (SSIs) and in Upper respiratory tract infections (URTIs), and the current scope of lincomycin use in these infections.

Methodology :

Computerized searches of the PubMed and Google scholar database were performed to identify primary and review articles about the therapeutic use of lincomycin between 2010 and 2020. Not many publications were found corresponding to this period. The search was then extended to include publications from 2000. Some articles published during the early years of its launch were also scanned to compare the change in bacterial sensitivity patterns over time. The keywords used during the search were 'lincomycin and skin infection', 'lincomycin and soft tissues infection', lincomycin and upper respiratory tract infections, and 'lincomycin review'.The articles were supplemented by examining cited references.

Efficacy of lincomycin in Skin and Soft Tissue Infections :

An early study in 1967 investigated the efficacy of lincomycin in the treatment of acute and chronic staphylococcalosteomyelitis and soft tissue infections[7]. It was a small cohort of 26 patients, comprising15 patients of osteomyelitis- 5 with the acute disease and 10 with thechronic form, and 11 with soft tissue infections. Most had not responded satisfactorily to various antibiotics,and many had

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undergone repeated hospitalization and one or more surgeries. Following the administration of lincomycin,all patients of acute osteomyelitis recovered completely with no adverse effects. Of the 10 patients with chronic osteomyelitis, 7 recovered completely and the other three improved slightly. Of the 11 patients withsoft-tissue infections, 7 patients recovered completely, 1 improved, and 3 showed nobenefit. Two of these 3 patients were infected with organisms found to be insensitive tolincomycin.Favourable results in similar cases were reported by Kanee B Geddes *et al* in 1964 also reported that from a clinical point of view the drug appears to be particularly valuable in the treatment of staphylococcal osteomyelitis[7]. Another early study in 1974 reported thatlincomycin administered at the start of clean neurosurgical procedures reduced the infection rate from 5.1 to 2.3%[8].

However, over the decades there has been a significant change in antibiotic practice, due to the high rate of resistance of many microorganisms to most antibiotics. Hence, the results of early studies might not be applicable to the current clinical practice. The more recent studies have reported different outcomes with lincomycin in various skin and soft tissue infections.

A study published in 2014 evaluated the efficacy of Lincomycin Hydrocloride 500 mg capsules /irrigation solution when used as an adjunct to scaling and root planning (SRP) and/or pre and post-surgical debridement in periodontal diseases in 42 patients[9]. The patients were prescribed Lincomycin Hydrocloride 500mg capsules orally thrice a day for 5 days. All patients who were diagnosed for gingivitis, and those who underwent pre-surgical and post-surgical periodontal procedures achieved complete relief, while 96.85% patients diagnosed for periodontitis achieved complete relief.

A study in 2013 in China, explored the role of lincomycin combined with heparin sodium in the prevention central venous catheter infection in the ICU [10]. A total of 172 patients who received central venous catheters were randomized into the trial and control groups with 86 cases in each group.The trial group received lincomycin and heparin sodium,and the control group received normal saline and heparin sodium.The incidence of infections in the trial group was 2.33% in 1-2 weeks after catheterization and 5.81% in 2-3 weeks after catheterization,and total incidence of infection was 9.30%.These were significantly lower than those in the control group (10.47%,15.12%,30.23% respectively), and there was statistical significance(P<0.05).The positive rate of blood culture in the trial group(12.50%)was significantly lower than that in the control group(53.85%); there was statistical significance (P0.05).

A retrospective study published in 2019 involved 60 patients with diabetic foot infections with or without osteomyelitis[11]. The patients were categorised as group 1-mild infection and group 2-moderate infection. Both groups were treated using local wound debridement and the systemic administration of antibiotics. Group 1 patients were treated with either of the two regimens, A (amoxicillin/clavulanate + metronidazole) and B (clindamycin + metronidazole), for 10-14 days. Group 2 patients were treated with either regimen A (ampicillin + cloxacillin + metronidazole) or B (lincomycin + metronidazole), for 6 weeks. In both groups, regimen B was prescribed for patients who were either allergic to penicillin or already on penicillin without a response. Group 1 showed an 80% cure rate under regimen A and a 100% cure rate under regimen B.Group 2 had a 61.5% cure rate under regimen A and 11.53% improved, while regimen B patients had a 68.75% cure rate and 12.5% improved. The study reported that intravenous lincomycin and oral metronidazole show a higher cure rate among moderate diabetic foot infection patients with or without osteomyelitis.

A study among 40 randomly allocated patients, evaluated the effect ofintra abdominal lavage with an antibiotic solution of lincomycin and gentamycin in normal saline in decreasing the risk of postoperative infectionsafter surgeries for colorectal cancer[12]. Group 1 patients underwent intra abdominal lavage with normal saline, followed by a second lavage with a gentamicin–lincomycin solution, while group 2 underwent lavage with normal saline.There was a significant difference between the two groups in the incidence of postoperative wound sepsis. (5% in group1 and 45% in group2). In group1, the only isolated organism was Pseudomonas. In group2, three cases had E. coli and two cases each had Pseudomonas, Klebsiella, and Enterobacter infections (Fig 1).

A study of 30 patients with different skin infections was performed in India in 2017.Patients were prescribed Lincomycin 500 mg orally twice/thrice a day for 14 days depending on the severity of infection. A good response was seen in most types of infections Fig 2[13].

In another Indian study about the efficacy of lincomycin against the strains of S. aureus isolated from various types of pyodermas in children, published in 2000, 75% strains of staphylococci were susceptible to lincomycin in vitro and 95% of the patients responded to 5-10 days treatment. Lincomycin was given to all these children in a daily dose of 30 mg/kg 5 - 10 days[14]. Lincomycin appears to be still effective in children.

Lincomycin has also been used for the treatment of acne. In an early study in 1965, 14 patients with carbuncles, furuncles, folliculitis, cellulitis, laryngopharyngitis, lymphadenitis, pyonychias and dermatitis infectiosa eczematoides were treated with lincomycin. In every instance the sensitivity test with respect to staphylococci and/or streptococci showed good inhibition with low MIC of lincomycin.

	Group 1 [n=20)(n(%)]	Group 2 [n=20)(n(%)]	χ^2	P
Wound sepsis				
Negatives	19 (95.0)	11(55.0)	8.533*	0.003*
Positives	1(5.0)	9(45.0)		
Intra-abdominal abscess				
Negatives	19 (95.0)	18 (90.0)	0.360	^{FE}P=1.000
Positives	1(5.0)	2(10.0)		
Isolated organism				
Pseudomonas	1(100.0)	2(22.2)	2.837	^{MC}P=1.000
Klebsiella	0 (0.0)	2(22.2)		
Enterobacter	0 (0.0)	2(22.2)		
E coli	0 (0.0)	3(33.3)		

*Signifant value *P less than 0.05 FE, Fisher exact test; MC, Monte-Carlo test*

Fig 1 — Comparison between the two studied groups according to wound sepsis, intra-abdominal abscess and isolated organism[12]

Lincomycin was very effective against coagulase-positive S aureus and against S.hemolyticus Type A[15].Topical application of lincomycin has also been used in the treatment of acne. Amulticentric, randomized, double blind, placebo controlled, clinical trial was conducted in India in 2003 wherein lincomycin hydrochloride in 2% gel form was prescribed to 200 patients with grade II and grade III acne. About 70% cases showed a good to excellent response, which was significantly more as compared to 23% in the placebo group[16].

Dormanesh *et al* in 2005,attempted to study the antibiotic sensitivity of methicillin-resistant S aureus isolated from various types of hospital infections in children. Overall, 255 clinical samples from various types of infections including blood (n = 40), UTIs (n = 60), respiratory tract infections (n = 55), superficial and post-surgical wounds (n = 50) and burn infections (n = 50) were collected. Susceptibility of Methicillin-resistant S aureus (MRSA) isolates was tested. The most effective antibiotics were imipenem, lincomycin, vancomycin, cephalothin, cotrimoxazole and clindamycin Fig 3[18].

Fig 3 Resistance of Methicillin Resistant Staphylococcus aureus Strains of Various Types of Clinical Infections in Pediatric Patients Against Commonly Used Antibiotics[18].

However, in another study of 1310 post-surgical wound swabs in 2011, only 50% of MRSA isolates were susceptible to lincomycin[19].

From the above evidences, it is obvious that the efficacy of lincomycin in skin and soft tissue infections varies between the studies. Perhaps, local variations in antibiotic resistance of organisms lead to these variations. Nevertheless, lincomycin still seems to be an effective therapy in conditions like periodontitis, perioperative preventive and curative therapy, and certain skin conditions like folliculitis. It is also indicated for patients who are intolerant to penicillin. Topical application of lincomycin for acne could be another regular indication.Its use in other deeper infections like osteomyelitis and diabetic foot might vary as many of the causative organisms might be highly resistant to several antibiotics. Hence, in such cases culture and sensitivity test is necessary before deciding antibiotic therapy.

Upper Respiratory Tract Infection :

An early study in 1965, tested the sensitivity of different strains of streptococci and staphylococci to lincomycin. Of the 165 strains of streptococci tested, 164 were found to be sensitive to lincomycin.

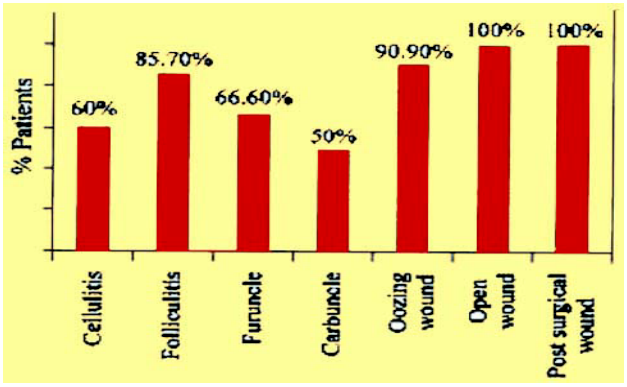

Fig 2 — Complete cure at the end of treatment[13]

Moreover, of the 3200 strains of staphylococci isolated from clinical material, only 40 were resistant to lincomycin. Nine of 14 patients with pneumonia, and 15 of 17 with acute exacerbations of bronchitis recovered completely with lincomycin therapy. Thirteen of the 14 patients of pneumonia had streptococcal infection. Notably, three patients showed partial resolution of the pneumonia with lincomycin but eventually resolved completely only when ampicillin was substituted for lincomycin after one week of treatment with lincomycin. Nevertheless, the authors reported that in the treatment of pneumonia and acute exacerbations of chronic bronchitis lincomycin appeared to be a satisfactory alternative to penicillin[21].

Later, Angeli et al. in 1997 compared the efficacy of lincomycin versus penicillin and clarithromycin in patients with acute pharyngitis/ tonsillitis caused by group A beta-hemolytic streptococci and in those

Antimicrobial Agents	Type of Infections, %					
	Blood (5)	UTIs (18)	RTIs(20)	Wound Infections(18)	Burn Infections(18)	Total (74)
Ampicillin	4(80)	15(83.33)	17(85)	16(88.88)	17(94.44)	69(93.24)
Centamycin	-	2(11.11)	6(30)	8(44.44)	8(44.44)	24(32.43)
Lincomycin	-	-	1(5)	2(11.11)	2(11.11)	5(6.75)
Cephalothin	-	3(16.66)	2(10)	1(5.55)	2(11.11)	5(10.81)
Imipenem	-	1(5.55)	-	1(5.55)	-	2(2.70)
Tetracycline	4(80)	16(88.88)	18(90)	17(94..44)	18(100)	73(98.64)
Vancomycin	1(20)	1(5.55)	1(5)	1(5.55)	1(5.55)	5(6.75)
Ciprofloxacin	1(20)	4(22.22)	3(15)	5(27.77)	5(27.77)	18(24.32)
Norfloxacin	1(20)	5(27.77)	5(25)	6(33.33)	7(38.88)	24(32.43)
Cotrimoxazole	1(20)	2(11.11)	2(10)	3(16.66)	4(22.22)	12(16.21)
Clindamycin	1(20)	2(11.11)	3(15)	3(16.66)	3(16.66)	12(16.21)
Trimethoprim-sulfa-methoxazole	1(20)	3(16.66)	6(30)	7(38.88)	9(50)	26(35.13)
Penicillin	4(80)	17(94.44)	18(90)	17(94.44)	18(100)	74(100)
Oxacillin	3(60)	15(83.33)	17(85)	16(88.88)	18(100)	69(93.24)
Erythromycin	2(40)	10(55.55)	12(60)	13(72.22)	15(83.33)	42(56.75)
Azithromycin	2(40)	8(44.44)	9(45)	12(66.66)	13(72.22)	44(59.45)
Ceftriaxone	1(20)	2(11.11)	3(15)	5(27.77)	5(27.77)	16(21.62)
Cefixime	1(20)	2(11.11)	5(25)	7(38.88)	7(38.88)	22(29.72)

Fig 3 — Resistance of Methicillin Resistant Staphylococcus aureus Strains of Various Types of Clinical Infections in Pediatric Patients Against Commonly Used Antibiotics[18]

with a clinical history of recurrence, in an open-label, prospective, randomized, comparative, single-masked study[22]. The study was conducted across 8 centres and they found that all drugs had statistically similar clinical and bacteriologic efficacy as well as tolerability.

In 2012, a randomized study in India involving 41 patients of tonsillitis/sinusitis showed that the overall response rate of lincomycin hydrochloride was more than that of cefpodoximeproxetil. 67.89% of the patients in lincomycin group and 52.27% in cefpodoxime group achieved complete relief, in all the clinical symptoms[24].

Another study from India in 2018, studied the bacterial pathogens and their antibiotic sensitivity pattern in 100 patients with chronic otitis media. 48.84% of the Pseudomonas aeruginosa (P aeruginosa) isolates, 50% of S aureus isolates, 88.89% coagulase-negative staphylococci were sensitive to lincomycin Fig 4[25]. This is an important finding considering that coagulase-negative staphylococci especially Staphylococcus epidermidis, are major nosocomial pathogens causing a variety of infections in humans[20].

Interestingly, in 2013 a report of 2 cases of acute myopericarditis associated with concomitant Streptococcus pyogenes [group A Streptococcus (GAS)] pharyngotonsillitis was published. After investigations, although no definitive pathogenesis could be explained, toxin-mediated myocarditis seemed to be the most popular explanation for this condition. One of the 2 cases who did not respond to penicillin, recovered completely with lincomycin[17].

A long-term studytested clinical isolates of Streptococcus pyogenes (S. pyogenes) obtained from a Lexington, Kentucky hospital in 2004 and again in 2014,for their sensitivity to macrolide antibiotics. Interestingly, 22% of the isolates from 2004 were resistant tolincomycin, while the resistance decreased to 11% in 2014[26]. A review was published in 2017 reported about the treatment challenges of Group A Beta-hemolytic Streptococcal Pharyngo-Tonsillitis (GABHS PT). It reported that lincomycin, clindamycin, and amoxicillin-clavulanate are more effective in relapsing GABHS PT[27].

From these results, theefficacy of lincomycin seems to be variable in different studies. However, lincomycin might still be effective in cases of URTIs not responding to the standard lines of treatment. It also seems to have an important role in GABHS PT. It must also be remembered though, that the results cannot be generalized, as the resistance patters can vary widely between different geographies and different centres.

Interestingly, a recent study compared the effectiveness of lincomycin and azithromycin in the treatment of COVID-19 associated pneumonia in a cohort of 24 patients. Bronchoalveolar-lavage PCR results were compared after treatment. On the 6th day after starting treatment, negative bronchoalveolar PCR result was seen in 83.3% patients in the lincomycin group and in 33.3% patients in the azithromycin group ($P < 0.05$). In addition, other clinical outcomes like duration of hospitalization, temperature normalization, and radiological progression were also better in the lincomycin group[28].

Adverse Effects of Lincomycin :

Lincomycin has been noted to produce an unusually high incidence of diarrhoea when given orally[32]. While several authors have noted the presence of mild to moderate diarrhoea after the use of lincomycin, others have described more severe diarrheal symptoms that clinically simulate acute ulcerative colitis or pseudomembraneous colitis[33]. However, no serious toxicity was reported during the clinical investigation of lincomycin in both UK and the United States (a total of approximately 2,500 patients)[34]. Similarly, none of the studies referenced above reported any severe adverse event. Some cases developed diarrhoea, which was controlled after reducing the dose of lincomycin.

Can Interchangeability of Lincosamides be Assumed in Clinical Practice ?

In 2010, the Australian therapeutic guidelines presented lincomycin and clindamycin as equivalent treatments for serious infections due to S. pyogenes, S Agalactiae and S Aureus[29]. A paper published in 2014, mentioned that parenteral lincomycin use now exceeds parenteral clindamycin use in hospitals, including intensive care units in Australia. NinetyS. pyogenes, 45 S.agalactiae, and 100 S aureus isolates (50 methicillin susceptible and 50 methicillin resistant) were tested for MICs of clindamycin and lincomycin. All S pyogenes and S aureus isolates tested, had similar susceptibilities for clindamycin and lincomycin. Three of the S. agalactiae isolates had an erythromycinsusceptible, low-level clindamycin-resistant pattern, but were susceptible to lincomycin[30].

Summary :

It is important to have local hospital-based knowledge of the organisms causing various infections and their antibiotic sensitivity

Bacteria	No	GM	AS	CF	CP	BA	TE	LE	OF	LM	CH	AK
Pseudomonas aerujinasa	43	41 (95.35)	35 (81.40)	37 (86.05)	29 (67.44)	12 (27.91)	21(48.64)	33(76.74)	22(51.16)	21(48.84)	41(95.35)	38(88.37)
staphylococcus aureus	12	9 (75)	9(75)	10 (83.33)	8 (66.67)	4 (33.33)	8(66.67)	7 (58.33)	6 (50)	6 (50)	-	9 (75)
CONS	9	9 (100)	9 (100)	9 (100)	9(100)	5 (55.56)	8 (88.89)	8 (88.89)	7 (77.78)	8 88.89)	-	9(100)
Klebsiella pneumoniae	7	7(100)	5 (71.43)	6 (85.71)	6 (85.71)	3 (42.86)	6 (85.71)	6(85.71)	4(57.14)	3 (42.86)	7 (100)	6 (85.71)
Escherichia colia	4	4 (100)	2 (50)	3 (75)	4 (100)	2 (50)	3 (75)	3 (75)	2 (50)	2 (50)	4 (100)	4 (100)
Proteusvulgaris	2	2 (100)	1(50)	2 (100)	2 (100)	0(0)	1 (50)	1 (50)	0 (0)	1 (50)	2 (100)	2 (100)
Proteus mirabilis	1	1 (100)	0 (0)	1 (100)	1 (100)	0(0)	1 (100)	0 (0)	0(0)	0(0)	1 (100)	1(100)
Streptococcus pneumoniae	1	1(100)	0 (0)	1(100)	0 (0)	0 (0)	1(100)	0 (0)	0 (0)	0 (0)	-	0 (0)

CONS: Coagulase-negative staphylococci, GM : Gentamicion, AS : mpicillin/sulbactam, CF : Cefotaxime, CP : Ciprofloxacin, BA Cotrimoxazole, TE : Tetracycline, LE : Levofloxacin, OF : Ofloxcin; LM : Linomycin, CH : Chloramphenicol, AK : Amikacin

Fig 4 — Antimicrobial sensitivity patterns of bacterial isolates[25]

patterns[21]. Lincomycin is still an effective therapy in conditions like periodontitis, perioperative preventive and curative therapy, and certain skin conditions like folliculitis. It is also effective in cases of URTIs not responding to the standard lines of treatment. Moreover, as seen from a recent review, lincomycin has an important role in GABHS PT infections and in cases of relapsing GABHS.

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